Montelukast for acute asthma exacerbation in children aged 5 - 15 years - A randomized, double-blind placebo-controlled study

A Dissertation submitted in partial fulfillment of MD Pediatrics examination of The Tamilnadu Dr MGR Medical University, Chennai to be held in April 2016

CERTIFICATE

This is to certify that the dissertation entitled "Montelukast for acute asthma exacerbation in children aged 5 - 15 years - A randomized, double-blind placebo controlled study" is a bonafide original work done by Dr.Rahul Reddy C during his academic term – April 2014 to March 2016, at the Christian Medical College, Vellore, in partial fulfillment of the rules and regulations of the degree of MD Paediatrics Examination of The Tamilnadu Dr. M.G.R Medical University, Chennai to be held in April 2016. This work was carried out under my guidance in the Department.

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Declaration Certificate

This is to certify that the dissertation titled "Montelukast for acute asthma exacerbation in children aged 5 - 15 years - A randomized, double-blind placebo controlled study" which is submitted by me in partial fulfilment towards M.D. Pediatrics Examination of the Tamil Nadu Dr M.G.R. University, Chennai to be held in April, 2016 comprises only my original work and due acknowledgement has been made in text to all material used.

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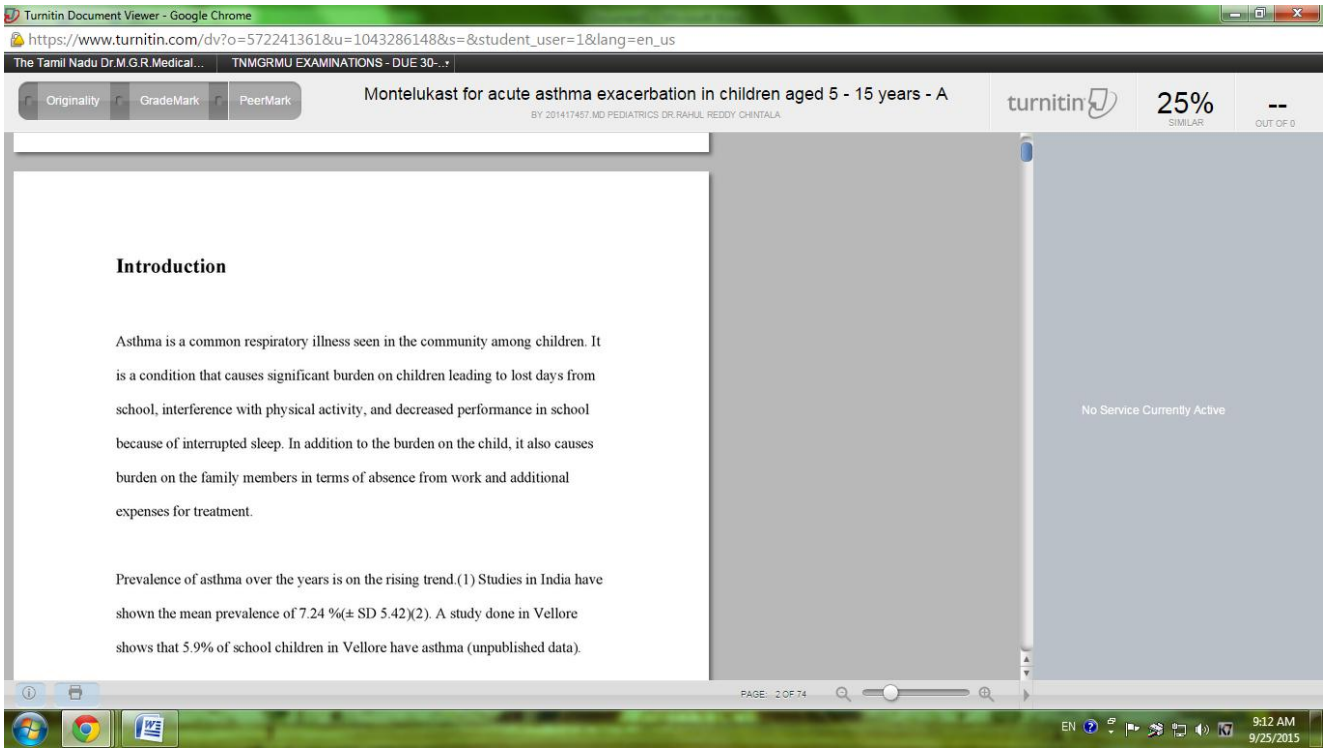
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Introduction
Asthma is a common respiratory illness seen in the community among children. It is a condition that causes significant burden on children leading to lost days from school, interference with physical activity, and decreased performance in school because of interrupted sleep. In addition to the burden on the child, it also causes burden on the family members in terms of absence from work and additional expenses for treatment.
Prevalence of asthma over the years is on the rising trend.(1) Studies in India have shown the mean prevalence of 7.24 %(± SD 5.42)(2). A study done in Vellore shows that 5.9% of school children in Vellore have asthma (unpublished data).
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Abbreviations

PEF/PEFR	Peak expiratory flow rate
LTRA	Leukotriene receptor antagonist
VAS	Visual analog scale
MPIS	Modified pulmonary index score
GINA	Global initiative for asthma
FEV1	Forced expiratory volume in 1st second
FVC	Forced vital capacity
LT	Leukotriene
CysLT	Cysteinyl leukotriene
LTC4	Leukotriene C4
LTD5	Leukotriene D4
PRAM	Pediatric Respiratory Assessment Measure
PIS	Pulmonary Index Score
PASS	Pediatric Asthma Severity Score
RAD	Respiratory rate, Accessory muscle use, and Decreased breath sounds
MDI-S	Metered dose inhaler with spacer
MDI	Metered dose inhaler
NAEPP	National asthma education and prevention program
Cmax	Mean peak plasma concentration
ICS	Inhaled corticosteroids
LABA	Long acting beta2 agonist
EIB	Exercise induced bronchoconstriction
ED	Emergency department
OPD	Outpatient department
DSMB	Data safety monitoring board
IRB	Institutional review board

Introduction

Asthma is a common respiratory illness seen in the community among children. It is a condition that causes significant burden on children leading to lost days from school, interference with physical activity, and decreased performance in school because of interrupted sleep. In addition to the burden on the child, it also causes burden on the family members in terms of absence from work and additional expenses for treatment.

Prevalence of asthma over the years is on the rising trend.(1) Studies in India have shown the mean prevalence of 7.24 %(± SD 5.42)(2). A study done in Vellore shows that 5.9% of school children in Vellore have asthma (unpublished data).

The underlying pathogenesis of asthma is a chronic inflammation of airway with reversible constriction of bronchial smooth muscle and mucus plugging. Multiple triggers such as viruses, toxins, pollen lead to exacerbations of asthma.

Management of asthma is directed towards reducing the inflammation of airway and reducing exposure to pro- inflammatory environmental factors and by controlling co-morbid conditions that can worsen asthma. Acute asthma

management focuses on symptom relief by correcting hypoxia, providing bronchial smooth muscle dilatation and treating inflammation.

Cysteinyl Leukotrienes are inflammatory mediators that play a key role in pathogenesis of acute and chronic asthma.(3–5) It has been observed that leukotriene excretion in urine is increased during an acute asthma exacerbation in children and adults(3), and this elevation in urinary leukotriene levels decreases as the asthma exacerbation resolves.(5) There are drugs that act to reduce leukotriene synthesis and prevent their action.

Montelukast is a leukotriene receptor antagonist. Hence, montelukast would act at the receptor level and reduce the action of leukotrienes. Monteleukast is used as preventer in the management of chronic asthma in adults and children. Other proven roles of montelukast are as symptom controller in children with moderate persistent asthma.(6) , in exercise induced asthma and asthma associated with allergic rhinitis.(7–9)

Several studies have been published evaluating the efficacy of leukotriene receptor antagonists in acute asthma in adults and children. However, based on currently available data, the role of montelukast in acute asthma in children is still unclear.

Hence, we conducted this placebo controlled clinical trial to evaluate the role of montelukast in acute asthma, by comparing the reduction in modified pulmonary index score between the two groups after study drug administration. Other parameters such as the need for steroid use, change in peak expiratory flow rate and subjective improvement in symptoms as assessed by child and parent using visual analog scale were compared between the two groups.

AIM AND OBJECTIVES

Aim

To assess the role of montelukast in the management of mild to moderate exacerbation of asthma in children aged 5-15 years.

Objectives

Primary outcome:

Reduction in Modified Pulmonary Index Score (MPIS) from baseline to 4 hours when montelukast (compared to placebo) is combined with standard management of mild to moderate exacerbation of asthma in children aged 5-15 years.

Secondary outcome:

Comparison between montelukast group and placebo group in

1) Improvement in peak expiratory flow rate from baseline to 4 hours and 36 -48 hours
2) Subjective improvement of symptoms using the visual analog scale by child and parent, from baseline to 4 hours and 36 -48 hours after study drug administration.
3) Change in modified pulmonary index score(MPIS) at 36-48 hours of study drug administration from baseline
4) Need for steroid use

LITERATURE REVIEW

Definition

Global Initiative for Asthma (GINA) defines asthma as *chronic inflammation associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.*(10)

Epidemiology

Asthma is one of the most common chronic diseases in the world. The highest prevalence of asthma and wheeze across the world was in Australia, New Zealand, Costa Rica and the United Kingdom.(1)

The ISAAC study which was a multi-country cross-sectional survey of two age groups of school children—6 to 7 years and 13 to 14 years showed prevalence of asthma follows a gradient of westernisation(1) and asthma is more in urban compared to rural areas.

Indian scenario

In India, the prevalence of asthma symptoms as per ISAAC Phase Three Study conducted between 1999 and 2004 (mostly 2002-03) was 6.8 compared to 6.2 at the time of ISAAC Phase One study done 5-10 years back. This was a multi-centre cross sectional survey performed with ISAAC questionnaire, which showed that the prevalence of asthma is on the rising trend in India.(1)

Study of prevalence of asthma in children of Bangalore in India showed a rising trend over many years.(11) Children from heavy traffic region suffered from asthma symptoms more than from low traffic area regions and asthma was more in urban areas compared to rural areas.(11)

A study conducted in and around Chennai in Tamil Nadu, revealed symptoms suggestive of asthma were present in 18% of children under 12 years of age.(12)

Although the prevalence of diagnosed childhood asthma was about 5% in both urban and rural areas, the prevalence of symptoms of breathing difficulty and nocturnal cough was significantly higher among urban children in the age group of 6-12 years(12).

Concept of asthma:

Criteria for making diagnosis of asthma are:

1. *History of variable respiratory symptoms* especially wheezing, shortness of breath, chest tightness, and coughing, often occur or worse at night or on awakening.

2. *Evidence of variable expiratory outflow limitation*, i.e., FEV1 and FEV/FVC is reduced, and variation in lung function is greater than in healthy people. FEV1 increased by more than 12% after inhaling bronchodilator, and average daily diurnal variability of PEF is >13% and FEV1 increased by >12% after four weeks of anti-inflammatory treatment.

Triggers for asthma symptoms are the following:

- air pollutants and exercise (13),
- thunderstorms(14)
- viral infections of respiratory tract (15)
- exposure to allergens

Clinical features of asthma:

The three classic symptoms of asthma which patients report are:

1. Wheeze
2. Cough
3. Shortness of breath or difficulty breathing

Some patients describe chest tightness or feeling of heaviness over the chest.

Some features that increase the probability of asthma are:

- Episodic symptoms – Asthmatic symptoms recur and resolve within hours to days, either spontaneously with the withdrawal of triggering stimulus or in response to anti-asthmatic medications. Symptoms that occur or worse at night is a feature of asthma.
- Characteristic triggers –Symptoms triggered by exercise, cold air, and exposure to inhaled allergens.

Pathogenesis of Asthma

- In a child with asthma, bronchoconstriction along with inflammation of the airways occurs.
- In the small airways, airflow is regulated by smooth muscle encircling the airways lumen.
- Inflammatory infiltrate and exudates consist of eosinophils and other inflammatory cell types (neutrophils, monocytes, lymphocytes, mast cells, basophils) and cause obstruction of the airways and desquamation into lumen.
- Pro-inflammatory cytokines (IL-4, IL-5, IL-13), and chemokines (eotaxin) mediate this inflammatory process. They are produced by Helper T lymphocytes and other immune cells.(16)
- Airway inflammation, airway hyper responsiveness, edema, basement membrane thickening, sub epithelial collagen deposition, smooth muscle and mucous gland hypertrophy, and mucus hypersecretion contribute to airflow obstruction.

Role of leukotrienes in asthma pathogenesis(17)

- Leukotrienes are produced in response to airway inflammation.
- Leukotrienes (LT) are metabolites of arachidonic acid.
- Membrane bound arachidonic acid is released by phospholipase A2.
- Free arachidonic acid is converted to prostanoids (prostaglandins, prostacyclin, thromboxane) by cyclooxygenase pathway or to *leukotrienes by 5 lipo-oxygenase pathway.*
- Two classes of leukotrienes are formed by the 5-lipo-oxygenase pathway, the non-peptide LTs- LTA4 and LTB4 and the *cysteinyl leukotrienes (Cys-LTs) LTC4, LTD4, and LTE4.*
- Cys-LTs are produced in mast cells, alveolar macrophages and eosinophils.
- Cys-LTs are potent bronchoconstrictor agents, about 100-1000 times more potent than histamine. (18)
- They enhance hyper responsiveness of airway, increase microvascular permeability and impair ciliary activity and play a role in airway re-modeling in chronic asthma.(19,20)
- These biological properties suggest that Cys-LT play a key biological role in asthma pathogenesis.

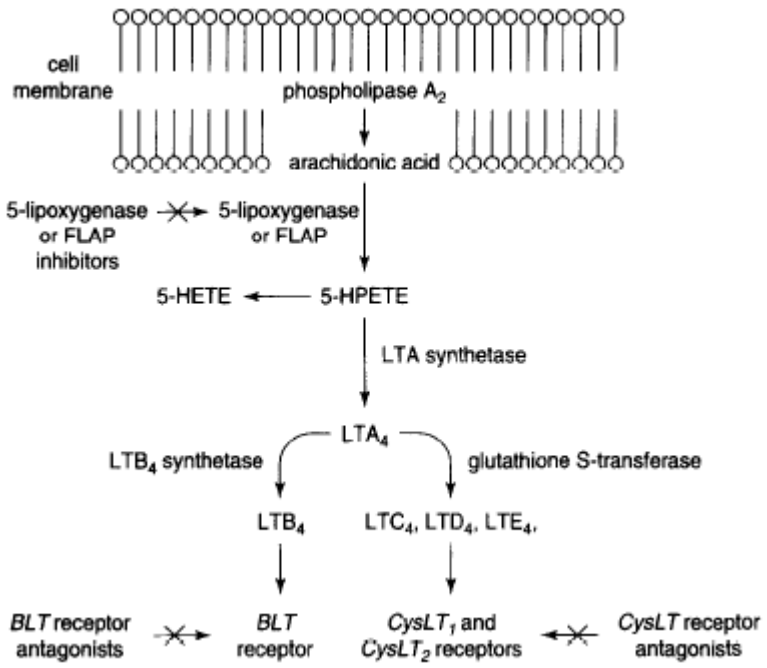


Figure 1. Steps in synthesis of leukotrienes.(17)

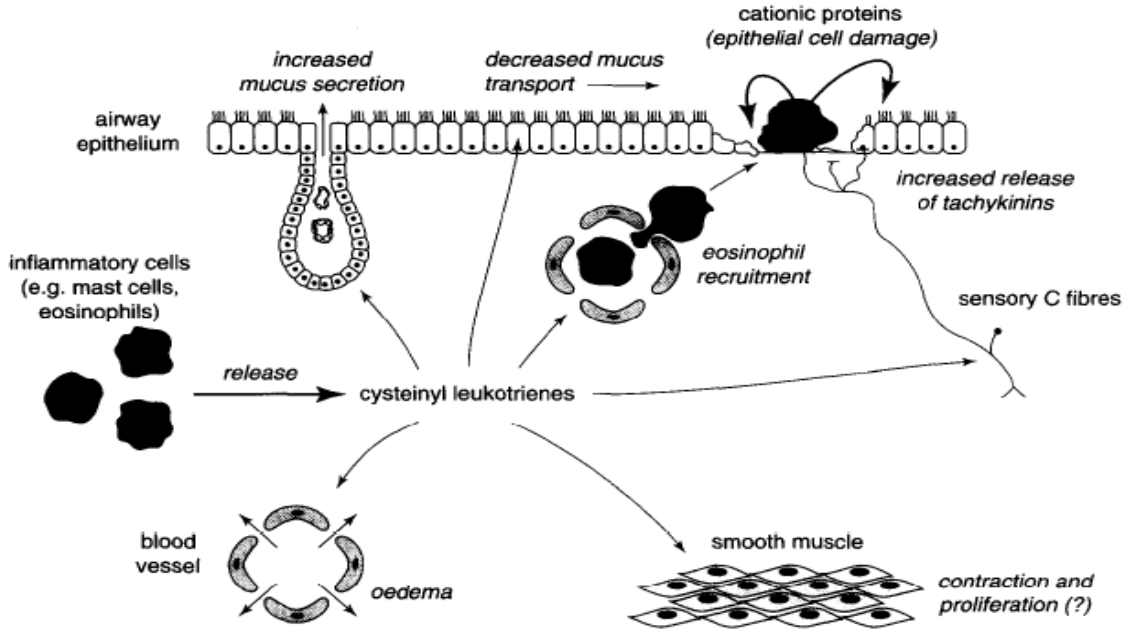


Figure 2. Sites of action and effects of cysteinyl leukotrienes in asthma.(17)

Drugs useful in asthma by acting on leukotriene pathway:

Two types of drugs:

1. 5-lipoxygenase inhibitors
2. Leukotriene receptor antagonist

Zileuton causes a decrease in leukotriene synthesis by blocking 5-lipoxygenase. Zafirlukast and montelukast are leukotriene receptor antagonists and act by blocking the receptor and prevent these mediators from causing their effect on the airways.

Actions of leukotriene receptor antagonists are:

1. Improvement in peripheral airway obstruction as assessed by pulmonary volumes, air trapping(21) and oscillometry(22).
2. Reduction in the number of eosinophils in induced sputum(23).
3. Reduction of eosinophil migration to lungs.(24)
4. Role in airway remodeling.(25)

Severity of asthma exacerbations:

Table 1: Clinical asssement of severity (Based on GINA guidelines,2011)(26):

	Mild	Moderate	Severe	Respiratory arrest Imminent
Breathless	Walking Can be down	Talking Infant-softer shorter cry: difficulty feeding Prefers sitting	At rest Infant stops feeding Hunched forward	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Respiratory rate	Increased	Increased	Often > 30/min	
Accessory muscles and suprastemal retractions	Usually not	Usually	Usually	Paradoxical thoraco-abdominal movement
Wheeze	Moderate, often noly end expiratory	Loud	Usually loud	Absence of wheeze
Pulse/min	< 100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent < 10 mm Hg	May be present 10-25 mm Hg	Often present > 25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
PEF after intial bronchodiator % predicted or % personal best	Over 80%	Approx 60-80%	< 60% predicted or personal best (<100L/min adults or response lasts <2hrs	

Asthma Severity Scores:

Several clinical asthma severity scores have been designed to evaluate the severity of initial exacerbation and to look for a response to treatment. It aids to assess the need for hospitalization.

1. **PRAM** score— The **P**ediatric **R**espiratory **A**ssessment **M**easure [PRAM] uses five variables: wheezing, air entry, saturation of oxygen, contraction of scalenes, suprasternal retraction.

PRAM score was validated against respiratory resistance measured by forced oscillation in children three to six years of age (27). It has discriminative value with good intra- and interrater reliability.

In a study done on children of 2 to 17 years with acute asthma, the PRAM score at triage and score after treatment with bronchodilators at 3 hours of treatment was strongly associated with hospitalization.(28)

Another study found a moderate level of discrimination between PRAM and length of stay >6 hours and/or hospitalization in children 18 months to 7 years (29). However, it was not found to be better than clinician assessment in predicting severity in another study(30).

2. **PIS** Score — The **P**ulmonary **I**ndex **S**core (PIS) is a scoring system taking into account five clinical variables: respiratory rate, saturation of oxygen, degree of wheezing, inspiratory to expiratory ratio, use of accessory muscle(31). Each variable is assigned a score from 0 to 3. Total scores range from 0 to 15.

A score of 7 to 11 indicates an exacerbation of moderate severity and a score of ≥12 indicates a severe attack.

The PIS is validated score and has been used as an outcome measure in several clinical trials(31–33). It can be used to assess initial severity and judge the response to treatment, and facilitate admission and discharge planning.(34)

3. **MPIS** score(35) - **M**odified **P**ulmonary **I**ndex **S**core is a modified version of PIS score. MPIS was developed at Connecticut Children's Medical Center and has been used since 1996 in pediatric asthma.

In the MPIS score, 6 categories are evaluated: oxygen saturation, accessory muscle use, inspiratory to expiratory flow ratio, the degree of wheezing, heart rate, and respiratory rate. For each of these 6 measurements or observations, a score of 0 to 3 is assigned. Heart rate measurement that was absent in PIS score is included in this.

It is useful for quantitative estimation of asthma exacerbation. A study conducted in 87 children with asthma during hospitalisation suggested utility of MPIS score in predicting clinical course after hospitalisation.(36)

A study showed that MPIS score had good inter-observer reliability and was showing good consistency and correlation with visual analogue scale assessed by physician.(37)

It is the first paediatric clinical asthma score that has been shown to have reproducibility and inter-rater reliability across different groups of health care professionals like physicians, nurses and respiratory therapists. In the same study, MPIS score at admission was found to have a correlation with severity of illness and duration of hospitalization and need for ICU stay. (35)

4. **PASS** score — The **P**ediatric **A**sthma **S**everity **S**core (PASS), which includes three clinical findings (wheezing, prolonged expiration, and work of breathing), was validated in a study of children aged 1 to 18 years.(38) It had discriminative value in deciding the need for hospital admission.

5. **RAD** Score— The **R**espiratory rate, **A**ccessory muscle use, and **D**ecreased breath sounds (RAD) score uses three clinical measures (respiratory rate,

accessory muscle use, and decreased breath sounds) and was useful in assessing severity of an acute asthma exacerbation in children aged 5 to 17 years.(39)

A prospective study was done in 2006-07 to evaluate the discriminatory ability Preschool Respiratory Assessment Measure (PRAM) and the Pediatric Asthma Severity Score (PASS) during an asthma exacerbation.(29), which showed that both PRAM and PASS scores appear to have good discriminative property. Both were able to predict admission but not need for a prolonged stay.

Management of acute exacerbations

Acute exacerbation of asthma can be classified into mild, moderate and severe based on GINA guidelines by clinical assessment (as described in Table 1) or can be classifiied based on asthma severity score. According to Pulmonary index score, score < 7 is mild, 7-11 is moderate and >/= 12 is severe(40).

Mild exacerbation — For children with mild asthma exacerbation,

Salbutamol inhalation therapy administered via nebulizer at a dose of 0.15 mg/kg (minimum 2.5 mg and maximum 5 mg per dose)(41) or metered-dose inhaler with spacer (MDI-S) at a dose of minimum two puffs and maximum eight puffs per dose(41–43) is used.

Repeated doses are given every 20 to 30 minutes(44) for three doses if needed, and the response is assessed.

Good response — If wheezing and breathing difficulty resolve after one to two beta agonist treatments, then the patient may continue with short acting beta agonist via metered dose inhaler or nebulisation given every four to six hours as needed at home.

Glucocorticoids are not routinely given to patients who respond to the initial dose or two of beta agonist.

Incomplete response — Patients who show an incomplete response to two beta agonist treatments or who have a history of severe or recurrent exacerbations in the past are given 10 to 20 minutes apart are initiated on systemic glucocorticoids.(45)

Moderate exacerbation — For children with moderate asthma exacerbation, administration of supplemental oxygen is advised if oxygen saturation ≤92 percent in room air(45). Salbutamol nebulization (0.15 mg/kg, maximum 5 mg) every 20 to 30 minutes for three doses.Ipratropium bromide (250 microgram/dose if <20 kg; 500 microgram/dose if >20 kg) every 20 to 30 minutes for three doses may be added(46,47).

Patients who have received three doses of intermittent therapy and showing incomplete response and require additional salbutamol therapy are treated intermittently every 30 to 45 minutes or may be switched to continuous therapy.(48–50)

Systemic glucocorticoids are administered soon after arrival or after the first inhalation therapy is initiated. Administration of intravenous magnesium sulfate (50 mg/kg, maximum 4 g is administered over 20 minutes), if there is lack of clinical improvement or clinical deterioration despite treatment with beta-

agonists, ipratropium bromide, and systemic glucocorticoids has shown benefit.(32)

Severe exacerbation — For children with severe asthma exacerbation,

Administration of supplemental oxygen if oxygen saturation is ≤92 percent in room air is required.(45)Salbutamol nebulization (0.15 mg/kg, maximum 5 mg) combined with ipratropium bromide (250 microgram/dose if <20 kg; 500 microgram/dose if >20 kg), every 20 to 30 minutes for three doses or continuously is used.

Patients who have received three doses of salbutamol in the first hour after ED arrival and require additional salbutamol therapy may be treated intermittently every 30 to 45 minutes or are switched to continuous therapy.(48–50)

Children with poor inspiratory flow or children who cannot cooperate with nebulized therapy or refractory to other medications are treated with epinephrine (0.01 mg/kg (max dose 0.5 mg) of (1:1000 Adrenaline) IM/SC); may be repeated after 15-30 min or terbutaline (0.01 ml/kg of a 1 mg/mL solution; maximum dose of 0.4 mg or 0.4 mL) administered intramuscularly or subcutaneously.(51–54)

Subsequent management depends upon response to initial therapy:

- For patients who improve after the initial treatment, the approach is as described above for moderate exacerbations.
- For patients with a poor response to initial treatment is as below:

•Administration of intravenous hydrocortisone 10 mg/kg IV stat and 2.5 mg/kg/dose IV every 6 hours or oral prednisolone 1-2 mg/kg/day in 2-4 divided doses or methylprednisolone (1 to 2 mg/kg, maximum 125 mg), which can be started as soon as intravenous access is obtained.

•Continuously nebulized salbutamol (alternatively, can be administered intermittently every 30 to 45 minutes).(48–50)

•Administration of intravenous magnesium sulfate (50 mg/kg, maximum 4 g administered over 20 minutes).(32)

For patients who do not respond to these interventions, administration of intravenous terbutaline(55) after completion of the magnesium sulfate infusion may be indicated: bolus with 10 microgram/kg over 10 minutes, then 0.3 to 0.5 microgram/kg/minute; infusion may be increased by 0.5 microgram/kg/minute every 30 minutes to a maximum of 5 microgram/kg/minute.

Monitoring — Frequent monitoring of respiratory rate, heart rate, oxygen saturation, the degree of alertness, accessory muscle use, and retractions is done.

Peak expiratory flow meter - It is useful to measure peak expiratory flow rate (PEFR) for monitoring. However, assessment of PEFR may have limited utility in the assessment of sicker or younger children.(56,57)

It is best if the child can make three attempts while standing (the best score is used), and it is most useful when it can be compared with the child's known personal best score(58).

Oxygen therapy — Children with moderate to severe acute asthma exacerbations have hypoxemia as a result of ventilation-perfusion (V/Q) mismatch, although in most patients, the hypoxemia is mild. Beta-agonists may worsen this mismatch by causing pulmonary vasodilation in areas of the lung that are poorly ventilated. (59)

Humidified oxygen should be provided as needed to maintain an oxygen saturation of ≥92 percent.(45) All nebulized medications are delivered with oxygen, generally at a flow rate of 6 to 8 L/min.

The role of antibiotics – No clear consensus is present on the need for antibiotics in asthma and evidence is currently insufficient.(60,61)Viral upper respiratory tract infections are the most common trigger. Use of antibiotics needed if the patient has a fever, leukocytosis, purulent sputum or radiographic infiltrates suggestive of an infection.

Glucocorticoids — Anti-inflammatory action of glucocorticoids reduces the airway edema effectively and decreases secretions associated with acute asthma exacerbations.(62)

Systemic glucocorticoids — The NAEPP guidelines suggest that oral administration of glucocorticoids is preferred to intravenous administration because oral administration is less invasive, and the effects are equivalent.(63)

However, for severely ill patients, intravenous access should be established, and intravenous hydrocortisone or methylprednisolone is administered.

Montelukast:

Mechanism of action: Montelukast is a leukotriene receptor antagonist.

Pharmacokinetics(64): Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (Cmax) is achieved three hours (Tmax) after administration in adults in the fasting state.(18,65,66) The mean oral bioavailability is 66%. The oral bioavailability and Cmax are not influenced by a standard meal.

For the 5 mg chewable tablet, the Cmax is achieved in two hours after administration in adults in the fasting state.(18,66,67)The mean oral bioavailability is 73% and is decreased to 63% by a standard meal.

After administration of the 4 mg chewable tablet to pediatric patients 2 to 5 years of age in the fasting state, peak plasma concentration is achieved 2 hours after administration.(65,68)

Side effect profile : Pediatric studies on montelukast found that it was well tolerated. Among children on daily use for chronic asthma, the majority of the reported adverse effects were mild and included headache, otitis media, diarrhoea, vomiting, nausea, abdominal pain and pharyngitis.(69)

Pooled data was collected from 11 multicentre, randomized, controlled montelukast Phase IIb and III trials and five long-term extension studies, with total of 3386 adult patients (aged 15–85 years) and 336 paediatric patients (aged 6–14 years) enrolled in the trials and 257 children among them received montelukast for up to 1.8 years. It showed that the incidence of adverse effects in both adults and children was not higher than with placebo. None of the adult and paediatric patients in these 11 montelukast clinical trials and extensions had vasculitis or churg strauss syndrome listed as a clinical adverse experience.(69)

There were concerns about mood and behavioural changes(70) and suicidal tendencies among children and adolescents(71), when montelukast is used long term but analysis of clinical efficacy studies have failed to confirm these adverse events. It is advisable for clinicians to screen for psychiatric morbidity before prescribing this drug for long term use.

No dose adjustment with montelukast is necessary for patients with renal and mild-moderate hepatic dysfunction.

Anecdotal reports suggest that even overdosage with monteleukast at doses of 80 mg montelukast in a 3 year old and 135 mg montelukast in a 5 year old did not lead to significant toxicity.(72)

Evidence and literature available for use of montelukast:

Monteleukast as preventer:

MONTELUKAST COMPARED WITH INHALED CORTICOSTEROIDS:

Greater efficacy of low-dose inhaled corticosteroids in comparison with montelukast has been shown considering specific outcomes (i.e. pulmonary function, symptoms or rate of exacerbations).(73)

All international guidelines suggest that inhaled corticosteroids are more effective than leukotriene receptor antagonists as monotherapy of asthma (6)

McIvor et al. in a recent study on 534 adult patients who had mild asthma which was well controlled with low-dose inhaled corticosteroids, showed that replacing inhaled corticosteroids with montelukast was associated with good asthma control in more than 75% of patients after 6 weeks, with an increase in compliance with treatment. (74)

Bufford et al. in a randomized controlled trial compared montelukast with inhaled fluticasone in 6-14 year old children with mild persistent asthma and results showed that montelukast was comparable to fluticasone in increasing the percentage of asthma rescue free days. However, secondary end points including FEV1, beta 2-agonist use, and quality of life improved significantly more in fluticasone treatment group.(75).

MONTELUKAST COMPARED TO LONG ACTING BETA AGONIST AS ADD ON THERAPY TO INHALED CORTICOSTEROIDS:

Pediatric studies comparing montelukast versus long acting beta2-agonist (LABA) as add on therapy to inhaled corticosteroids in persistent asthma are few in number. Buchvald et al. found that FeNO levels were significantly higher after salmeterol add on treatment than montelukast. FEV1 levels were comparable between the two groups(76).

A Cochrane review conducted among 6030 adults from eleven randomized controlled trials concluded that for asthmatics inadequately controlled on low doses of inhaled steroids, the addition of long acting beta2 agonist (LABA) is superior compared to leukotriene receptor antagonist for improving lung function, symptoms, and reduce use of rescue beta2-agonists and need for systemic steroids.(77)

MONTELUKAST IN EXERCISE INDUCED BRONCHOCONSTRICTION:

During exercise, evaporation of water from the airway surface is the stimulus for release of inflammatory mediators such as histamine and cysteinyl leukotrienes, which play a role in bronchoconstriction. Cysteinyl leukotrienes are the most important mediators in exercise induced bronchoconstriction (EIB).

Peroni et al. studied the timing of onset and duration of action of montelukast compared to placebo on exercise induced asthma in 19 child subjects. Patients were subjected to three consecutive treadmill exercise tests at 2, 12, and 24 hours after a single dose administration. The maximum protective effect with montelukast was observed after 12 hours of administration as assessed by percentage fall in FEV1.(8)

ROLE OF MONTELUKAST IN SEASONAL ALLERGIC RHINITIS:

In a study done on adults by Philip et al, once daily dosing of montelukast showed improvement in rhinitis symptoms and sneezing scores.(78) The same results were seen in the paediatric population in a study in India.(79) Beneficial effect on both daytime and night time symptoms were observed by as early as the 2nd day of daily therapy in a study by Weinstein et al.(80)

Razi et al. showed that montelukast treatment provided significant improvement in symptoms and peripheral eosinophil counts of school age children with seasonal allergic rhinitis but did not show a significant effect on eNO levels.(81)

ROLE OF MONTELUKAST IN OTHER CONDITIONS:

The potential role of montelukast in RSV bronchiolitis and potential in preventing post-bronchiolitis reactive airway disease is being currently under investigation. Bisgaard et al. in a randomized placebo controlled trial conducted in 130 infants, 3-36 months of age, have given either montelukast or placebo for 28 days starting

from 7 days of onset of acute RSV bronchiolitis symptoms and showed that infants on montelukast had more number of day and night symptom-free days compared with placebo group and also had significantly delayed daytime cough and exacerbations when compared with placebo.(82)

Montelukast in acute asthma

The following studies have been done on role of montelukast in acute asthma:

1. Harmanci et al. (83) conducted a randomized double-blind, placebo-controlled, parallel-group study to look at the safety and effectiveness of a 4-mg tablet of oral montelukast in addition to short-acting beta2-agonist as the initial treatment in mild to moderate asthma exacerbations in **children between 2 and 5 years old**. Fifty subjects who were between the ages of 2 and 5 years who were using only short-acting beta2-agonists on demand and who had a clinical history of intermittent asthma were included. The outcome assessed was reduction in pulmonary index score and need for steroids. This study showed a beneficial effect as there was reduction in pulmonary index score and reduction in need for steroids in mild to moderate acute asthma in preschool-aged children when single dose of 4 mg montelukast was administered concomitantly with short-acting beta2-agonist bronchodilators as the initial treatment.

2. Nelson et.al(84) conducted a randomized, double-blind, placebo-controlled study with study subjects being **children aged 6 to 14 years** with moderate acute asthma exacerbations (peak expiratory flow rate, 40%-70% predicted) presenting to emergency department of a tertiary care urban centre.

A total of 26 subjects were randomized and received montelukast 5 mg or placebo orally in addition to standard therapy and the primary outcome of predicted change of FEV1% at 3 hours was looked into. After interim analysis, which showed that oral montelukast (5 mg) added to standard therapy did not result in additional FEV1 improvements in 3 hours, this study was concluded.

3. Todi et.al.(85) conducted a double-blind randomised controlled trial in Emergency room and outpatient paediatric services at AIIMS Hospital, New Delhi, a tertiary care center, to study the effect of the addition of a single dose of oral montelukast to standard therapy in acute moderate to severe asthma.

117 **children aged 5-15 years** (without prior use of montelukast) with acute moderate to severe asthma exacerbation, as defined using Modified Pulmonary Index Score (MPIS) $\geq$ 9 were enrolled.

Children received montelukast (5-12 years: 5 mg and >12 years: 10 mg) or placebo orally in addition to the standard therapy. In this study, the primary outcome was reduction in MPIS to less than 9 at the end of 4 hours. They also

assessed FEV1 improvement from baseline to 4 hours.There was no significant difference in outcomes measures. All children had received systemic steroids in this study. The authors suggested the use of a higher dose of the drug and for longer duration in further trails. No adverse events occurred during this study.

4. Morris et al**(86)** in California conducted a randomized, double-blind, placebo-controlled, multicenter study of **children aged 6 to 14 years** between 2005 to 2008 to study the role of *intravenous* montelukast in children with acute asthma.

Subjects with an FEV1 of 75% or less of the predicted value after up to 120 minutes of standard therapy were included in the study and 276 subjects were randomized to intravenous montelukast 5.25 mg (n=145), or placebo (n=131) added to standard therapy.

The primary end point measured was the time-weighted average change in FEV1 during 60 minutes (deltaFEV1 [0-60 min]). Secondary end points looked into were the percentage of patients who required hospitalization after drug administration and the change from baseline in modified pulmonary index score(MPIS) after 60 minutes of treatment. The study results showed that montelukast was not significantly more effective than placebo for delta FEV1 [0-60 min] when added to standard therapy. No significant differences were found in the percentages of patients in whom treatment failed or the modified pulmonary index score after 60 minutes. Both treatments were well tolerated.

6. Dockhorn et al.(87) conducted a double blind, placebo controlled, three period cross over randomised controlled trial. 51 **adult subjects** (FEV1 40–80% predicted and >15% improvement after inhaled beta agonist) were included in the study. Results showed that the onset of action for intravenous montelukast was faster than for oral montelukast and the improvement in airway function lasted over the 24 hour observation period for both treatments. The onset of bronchodilation with both the intravenous and oral formulation of montelukast was 15 and 120 minutes, respectively. There was also a trend toward a greater improvement in FEV1 with intravenous than with oral montelukast.

7. Camargo et al.(88) conducted a placebo controlled randomised controlled trial comparing 7 mg of *intravenous* montelukast with placebo in addition to standard care among 583 **adults**. The primary endpoint was the time-weighted average change in FEV1 during 60 minutes after drug administration. Intravenous montelukast was found to be effective and produced significant relief of airway obstruction throughout the 2 hours after administration, with an onset of action as early as 10 minutes.

8. In a **Cochrane systematic review**(89) to asssess effectiveness of adding an oral leukotriene receptor antagonist (LTRA) to standard treatment for the management

of acute asthma in **adults and children** in the emergency department, wherein 10 studies involving 1940 patients were included, results failed to demonstrate a statistically significant or clinically important reduction in need for hospital admission in children. There was a statistically but not clinically significant difference in FEV1 in the adult studies.

Justification of our study :

We postulated that in mild to moderate exacerbations, montelukast may have a role in bringing the symptoms under control which can be measured by objective criteria like modified pulmonary index score(MPIS) and peak expiratory flow rate (PEFR) and subjective criteria like visual analog scale by child as well as parent.

Visual analog scale as an outcome measurement tool:

Visual analog scale(VAS) has a role as an initial tool to assess the bronchodilator response in children with asthma and has been proven useful in assessing and monitoring of severity of asthma (90,91). Measurement of VAS measurement in asthma was able to discriminate between patients with "controlled," "partly controlled," and "uncontrolled" asthma and correlated with GINA-defined categories and can be a simple guide in evaluation of asthma control(92). We decided to use this tool as a measurement of subjective improvement by parent and child. We believe child returning back to school, and caretaker reporting back to work will depend on this.

Use of higher dose of montelukast:

We used a higher dose of the drug (two doses of 10 mg for less than twelve years and 20 mg for more than twelve years, 24 hours apart) than routinely used for daily treatment. Use of a higher dose of montelukast for acute asthma was suggested by the authors of a similar study done in AIIMS , New Delhi.(9) Reiss et.al in an adult study reported the benefit of oral montelukast in doses that were relatively high (montelukast 100 and 250 mg compared with standard daily doses.(93) We anticipated a dose-dependent response in improvement if higher oral montelukast doses are administered in children too. It was considered safe based on anecdotal reports where overdosage with monteleukast at doses of 80 mg montelukast in a 3 year old and 135 mg montelukast in a 5 year old did not lead to produce significant toxicity.(72)

MATERIALS AND METHODS

Materials and Methods

Design: This is a prospective, double blind, randomized placebo controlled trial.

Setting: Study was done in a tertiary care pediatric hospital in south India.

Participants: All children aged 5-15 years with clinical diagnosis of asthma who presented with mild to moderate exacerbation and satisfied the inclusion criteria during the study period (9^{th} February 2014 to 15^{th} September 2015 over a duration of 7 months) were included in the study.

Inclusion Criteria:

Children aged 5-15 completed years with a diagnosis of asthma presenting with mild to moderate acute exacerbation (modified pulmonary index score 5-11)

Exclusion Criteria:

1) Severe exacerbations with a modified pulmonary index score >12.
2) Children who have been already started on oral steroids for present exacerbation
3) Children on treatment with daily montelukast in the last month
4) Children who cannot remain in hospital for atleast 4 hours from the onset of treatment.

Note: Prior inclusion in this study > 6 weeks before was not an exclusion criteria.

Target sample size and rationale:

In a pilot study that was undertaken, we had observed that 60% of children with acute mild to moderate excerbation of asthma receiving standard therapy had a reduction in MPIS score of 4 or more at the end of 4 hours. For the power of the study to be 80%, an α error of 5% (two-sided) and estimated proportion of children who achieve an MPIS reduction of 4 or more at the end of 4 hours as 85% with montelukast (compared to 60% with placebo i.e. a difference of **25%**) ,sample size was estimated to be 49 in each group. Assuming a drop out of 5%, 52 patients will be needed in each arm.

Statistical analysis:

Statistical analysis was done using SPSS software for data analysis. The mean and standard deviation and median are used as the representatives of the measurements among placebo and montelukast groups. The statistical significance between the two groups were tested using independent sample t test. For non-normal data, Mann-Whitney U test is used to compare the two groups. The proportions among the two groups were compared by using Chi square test. When the cell frequencies were less than 5, Fisher's exact test was used.

Institution review board and Ethics committee approval: The proposal was accepted by the Institutional review board and Ethics Committee of the institution. The proposal

was presented to the committee, queries raised by the committee were clarified, and permission was obtained. (APPENDIX VII)

Funding: Expenses related to this research project were met by the fluid research grant of Christian Medical college Hospital. No part of the study was sponsored by pharmaceutical companies.

CTRI trial registration:

Following the Institution review board and Ethics Committee approval, the trial was registered at the clinical trials registry (CTRI/2015/01/005423 on 19/1/2015) (APPENDIX V)

Randomisation and allocation concealment:

Statistician prepared a computer generated block randomization table with block size of 10.(APPENDIX XII)

Randomisation table prepared by statistician was handed over to the pharmacist, who prepared the study drugs (monteleukast or placebo in syrup form), and these were numbered serially. Order of randomization was not available to the investigator.

Preparation of study drug

According to the randomization scheme, hospital pharmacists independently prepared study medications (drug and placebo). Pharmacy purchased study drug monteleukast and dispensed in a syrup form following a standard operating procedure (APPENDIX XIII).Placebo syrup also was prepared in the hospital pharmacy.

Each aliquot contained 10 mg drug in 10 ml syrup. This ensured that parent did not have to divide the aliquot to give the required dose which in turn may lead to loss of drug during administration. Parent was given simple instruction to give 1 or 2 aliquots as per weight of child.

Placebo and active drug were indistinguishable in volume, color, consistency, and taste. (APPENDIX X) Medications were prepared in batches to ensure the stability of drug over time. Concentration of drug in the formulation was checked by an independent lab and was found to be correct. (APPENDIX IX)The study medication was stored in the ED/OPD at room temperature for quick access after enrollment.

In the treatment arm, child between 5-12 years received 10mg of monteleukast i.e. 1 aliquot of 10 ml at 0 hour and 24 hour each, while child > 12years received 20

mg i.e. 2 aliquots of 10 ml at 0 hour and 24 hour each. In the placebo arm 1or 2 aliquots of the 10 ml placebo syrup were given for the two age groups respectively.

Blinding and masking:

Principal Investigator, subjects, nurses, and physicians were blinded to treatment assignment.

Methods:

This study was conducted on children with asthma aged 5-15 years who satisfied the inclusion criteria. After initial triage assessment in the emergency department or outpatient unit, parents were contacted by principal or co - Investigator.They were briefed about the study and invited to participate. An informed consent was obtained from the parent and an assent from the child (children above 12 years).

Details of the present illness, past history, treatment and family history were collected using a structured clinical research form. Baseline clinical parameters including anthropometric and vital signs were recorded. The Modified pulmonary index score was recorded (APPENDIX.VI).Peak flow was recorded using Wright's peak flow meter (in litre/min) using best of three attempts. Visual analog scale was shown to the parent and

child and explained. Child and parent marked this independently and the value in millimeters was noted by the investigator.

Inhaled bronchodilators +/- systemic steroids and oxygen as per standard protocol for treatment of asthma exacerbations was administered as decided by treating physician. This was initiated at any of the above steps without any delay as deemed necessary by treating physician. Record of the treatment received was maintained.

Following the randomization allocation, first dose of study drug was administered within 1 hour of the initiation of treatment. In the treatment arm, a child between 5-12 years received 10 mg of montelukast in syrup form at 0 hours and 24 hours while child > 12years were given 20 mg at 0 hours and 24 hours.In the placebo arm, the child received a syrup that is similar in taste, colour and volume at 0 hours and 24 hours. The Principal investigator reminded parents by phone about the second dose which was to be given at 24 hours if they were discharged home.

Children were monitored using MPIS, PEF and visual analog score (by parent and child) at 4 hours. After 4 hours, study subjects were discharged home or admitted to ward/ casualty. Parents were advised to continue treatment with salbutamol inhaler at home and record the frequency of use.

A follow up visit was arranged between 36 to 48 hours of study drug administration .At this point, outcome variables were again measured. At all points, any adverse event was recorded.

Second follow up visit was scheduled in asthma clinic when the child was completely well (as is the standard of care).At this visit, PEF was checked again and was taken as personal best.

Data Safety Monitoring Board (DSMB) review:

Adverse effects after administration of study drug were monitored. All data was submitted to the Institutional Data Safety Monitoring Board for review during the trial. Approximately 6 months after the recruitment of the first patient, DSMB board met and reviewed the records of adverse events. At that point, 1 out of 20 patients recruited had a minor side effect of vomiting. Study was allowed to continue.(APPENDIX XI)

RESULTS

Randomised placebo controlled study was done to investigate the role of monteleukast in acute asthma by assessing it's effect on bronchodilatation and symptom relief during mild to moderate exacerbation of asthma in children. Patient recruitment was done during the period February 2015 to September 2015. In total, 30 patients with acute asthma exacerbation were screened for eligibility. A total of 22 subjects were enrolled and randomised, 11to the montelukast group and 11 to the placebo group.

None of the patients withdrew after randomisation. No patient was lost to follow up. Two patients did not receive the second dose of the drug due to minor adverse drug reaction. Data from all 22 subjects was analysed under intention to treat analysis.

Since the required sample size was not met, results of an interim analysis are presented below.

Consort flow diagram of the trial:

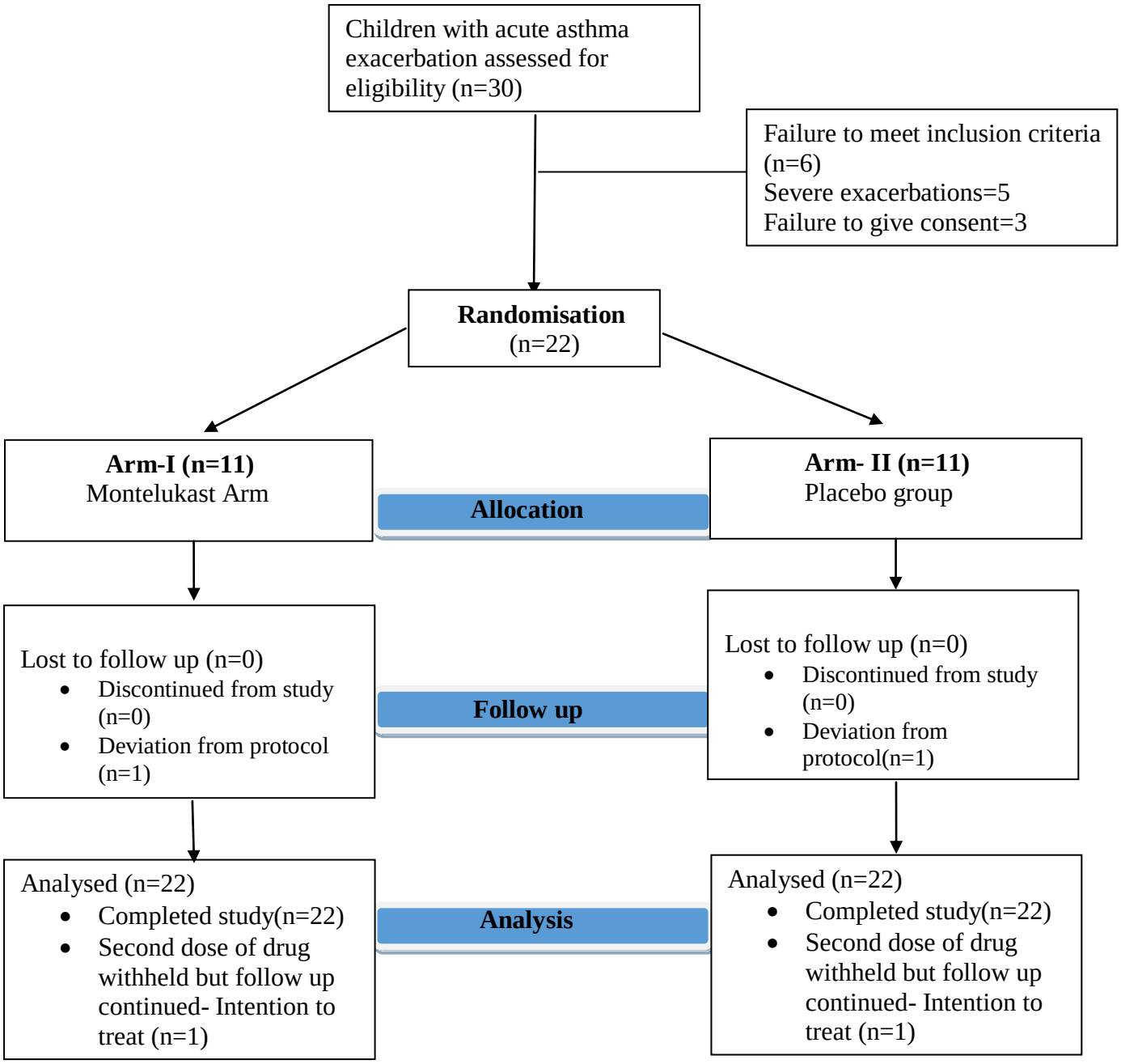


Table 2: Demographic characteristics of montelukast and placebo group

Characteristic	Montelukast group (N=11)	Placebo group (N=11)
Age (Mean ± SD)	10.55 ± 2.38	8.36 ± 2.50
Sex: Male: n (%) Female: n (%)	8(72.3%) 3(27.3%)	10(90.9%) 1(9.1%)
Age of onset of asthma symptoms (median):	2 years	2 years
Duration of current exacerbation:	2 days	2 days
Preceded by URTI Yes No	8(72.3%) 3(27.3%)	10(90.9%) 1(9.1%)
On inhaled steroids during exacerbation Yes No	 4(36.4%) 7(63.6%)	 4(36.4%) 7(63.6%)
History of allergic rhinitis Yes No	 2(18.2%) 9(81.8%)	 2(18.2%) 9(81.8%)
Family history of asthma Yes No	 2(18.2%) 9(81.8%)	 6(54.5%) 5(45.5%)
Baseline Modified pulmonary index score (mean)	8.09	7.36
Number of children who had Sp02 of </= 92% at admission	3	0

Patients enrolled in the two groups were comparable in terms of demographic features like age, duration of asthma symptoms, duration of current exacerbation,

history of allergic rhinitis and ongoing inhaled steroid use as a preventer. The severity of the exacerbation as assessed by the Modified pulmonary index at baseline was comparable. However in the placebo group there were more boys and more patients with family history of asthma . More patients in the monteleukast group were hypoxic at baseline.

Table 3. Comparison of severity of exacerbation of asthma at baseline

	Montelukast group n (%)	Placebo group n (%)	P value
Mild exacerbation (PIS <7)	4 (36%)	8 (72%)	>0.99
Moderate exacerbation (PIS 7-12)	7 (64%)	3 (28%)	
Total	11(100%)	11(100%)	

The number of subjects with moderate exacerbation of asthma was more in montelukast group, implying that children assigned to montelukast group were sicker at presentation. This difference is not statistically significant.

Assessment of primary outcome of the study

Reduction in Modified Pulmonary Index Score (MPIS) from baseline to 4 hours after montelukast compared to placebo when combined with standard management

Table 4. Proportion of children who had ≥4 MPIS score reduction at 4 hours in both groups

	Children with ≥ 4 MPIS score reduction n (%)	Children with < 4 MPIS score reduction n (%)	P value
Montelukast (N=11)	**8 (72.7)**	3 (27.3)	0.50
Placebo (N=11)	**7 (63.6)**	4 (36.4)	
Total	**15**	7	

Children with MPIS score reduction of more than 4 at four hours was more in montelukast group. The result was not statistically significant. It is shown below as a bar diagram.

Figure 3: Comparison of proportion of subjects who achieved target MPIS score reduction

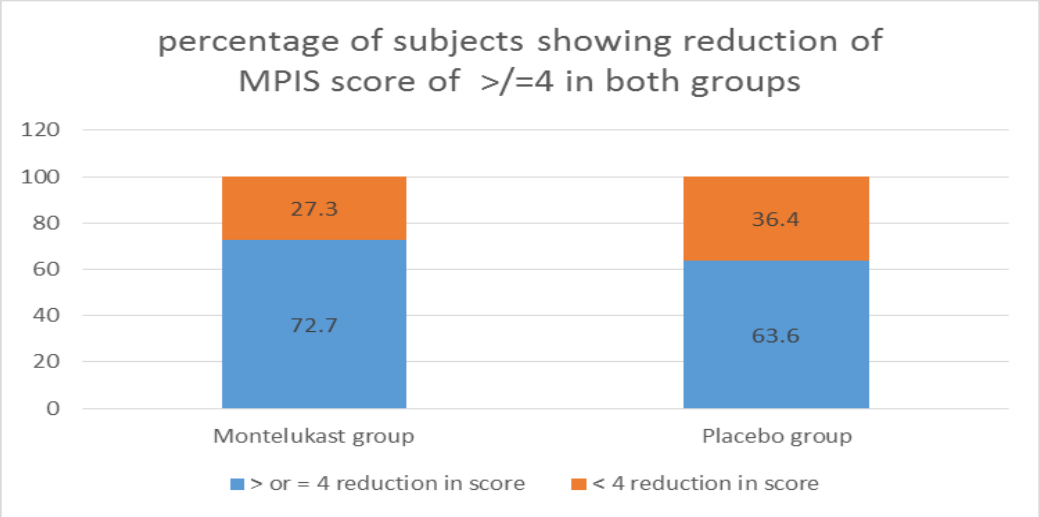


Table 5. Comparison of mean reduction in MPIS score at 4 hours of drug administration from baseline score

	Reduction in MPIS score at 4 hours from baseline score Mean(±SD)	P value
Montelukast (N=11)	**4.73 (2.00)**	0.293
Placebo (N=11)	**3.82 (1.94)**	

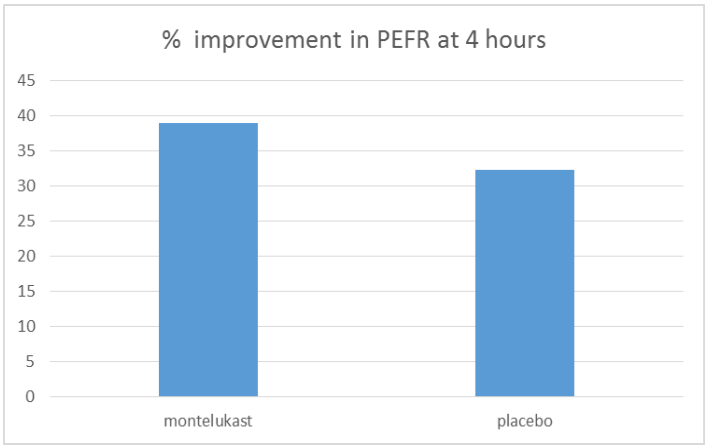
There was no statistically significant difference between the two groups in the proportion of subjects who achieved the target reduction in MPIS score. Mean reduction in the score from baseline also did not show a statistically significant difference between the two groups.

Assessment of secondary outcomes of the study

1. *Improvement in peak expiratory flow rate (PEFR) at 4 hours and at 36-48 hours*

Table 6 & Figure 4. Comparison of percentage improvement in peak expiratory flow rate (PEFR) at 4 hours

	Percentage improvement in PEFR at 4 hours Mean% (± SD)	P value
Montelukast (N=11)	38.88 (± 34.77)	0.62
Placebo (N=11)	32.22 (± 28.44)	

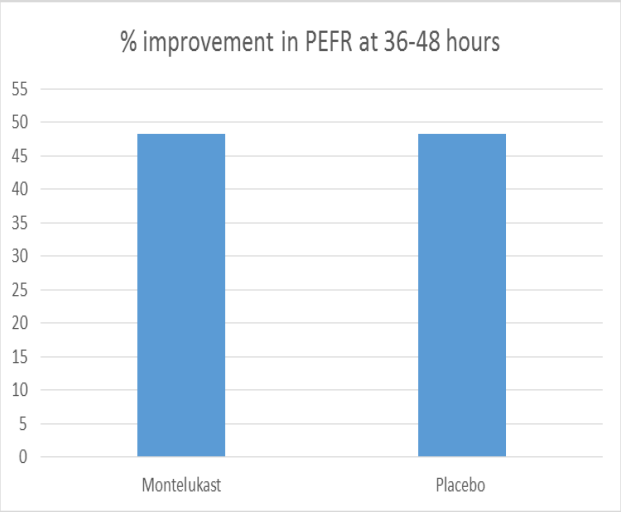


Percentage improvement in PEFR at 4 hours was calculated as (PEFR at 4 hrs-PEFR at baseline) / PEFR at baseline. Both groups recorded a clinically significant

improvement, which is >20%. However, between the treatment and placebo arm, there was no statistically significant difference in improvement.

Table 7 & Figure 5. Comparison of percentage improvement in peak expiratory flow rate (PEFR) at 36 - 48 hours

	Percentage improvement in PEFR at 36-48 hours Mean % (± SD)	P value
Montelukast (N=11)	48.19 (± 38.49)	>0.99
Placebo (N=11)	48.30 (± 28.80)	



Percentage improvement in PEFR at 36-48 hours was calculated as (PEFR at 36-48 hrs - PEFR at baseline) / PEFR at baseline. The percentage improvement in PEFR at 36-48 hours was similar in both arms.

Table 8. Comparison of proportion of subjects with peak expiratory flow rate (PEFR) of ≥ *80% of personal best* when assessed at 36-48 hours (N=17)

	Children with PEFR *≥80% of personal best* n (%)	Children with PEFR *< 80% of personal best* n (%)	Total
Montelukast	6 (75%)	2(25%)	8(100%)
Placebo	6 (66.7%)	3(33.3%)	9(100%)
Total	12	5	17

P value >0.99

Only in 17 subjects, *personal best of PEFR* was available, 8 in monteleukast and 9 in placebo group. By 36-48 hours, majority of patients in both groups had PEFR ≥ 80% of their personal best.

2. Assessment of improvement at 4 hours and 36-48 hours using visual analog scale (VAS) by parent and child

- Mean baseline visual analog scale measurement for montelukast and placebo group was 43.6 mm and 34.5 mm respectively. Change from baseline was assessed at 4 hours and 36 hours and is expressed in millimeters below.

Table 9. Improvement in Visual analog scale from baseline to 4 hours assessed by parent and child

	Mean improvement (in millimetres) of VAS by **parent** at 4 hours of drug (± SD)	Mean improvement (in millimetres) of VAS by **child** at 4 hours of drug (± SD)
Montelukast group (N=11)	37.3 ± 18.4	39.1 ± 25.4
Placebo group (N=11)	27.3 ± 17.9	24.5 ± 11.2
P value	0.21	0.10

Table 9 shows that when visual analog scale was used to express subjective improvement, both parent and child recorded similar increment by 4 hours. The difference between the montelukast and placebo group was not statistically significant. These findings are represented below.

Figure 6. Improvement in Visual analog scale from baseline to 4 hours assessed by parent and child

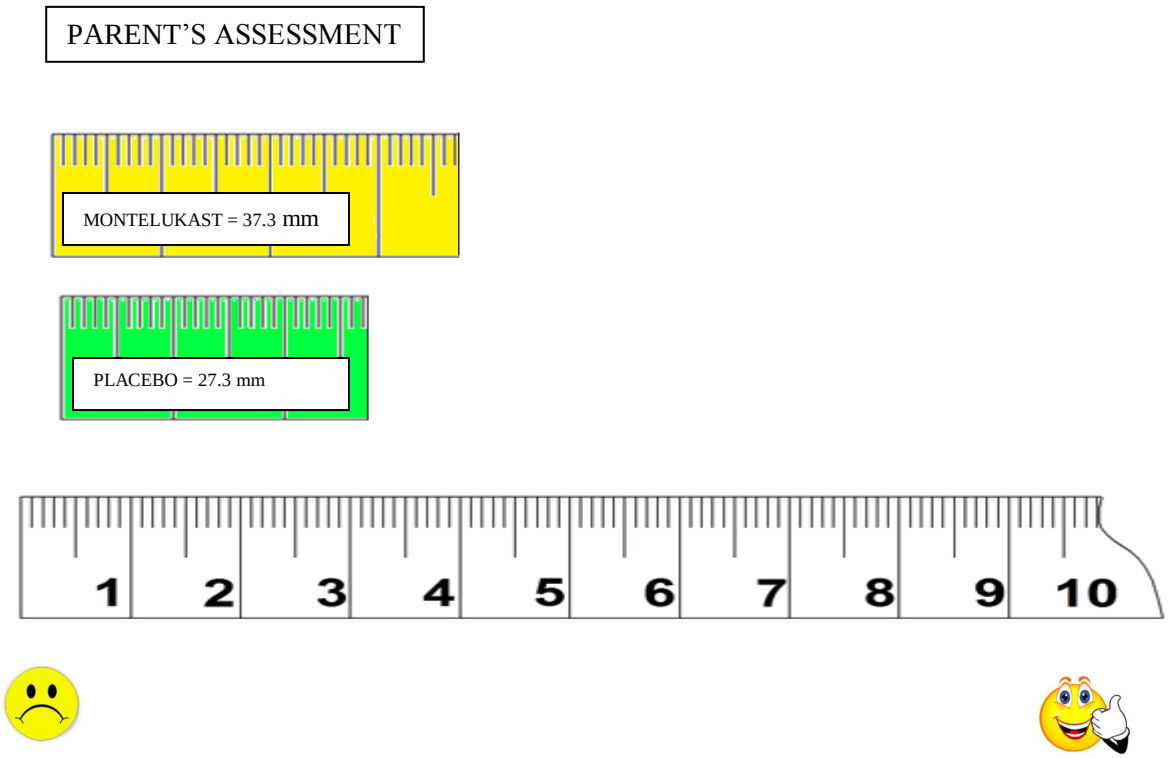


Figure 6 shows the mean improvement in millimetres in Visual analog scale according to parents and child at 4 hours was more in montelukast group compared to placebo group.

Table 10. Improvement in Visual analog scale from baseline to 36-48 hours assessed by parent and child

	Mean improvement (in mm) of VAS by **parent** at 36-48 hours of drug	Mean improvement (in mm) of VAS by **child** at 36-48 hours of drug
Montelukast group (N=11)	52.7 ± 21.0	53.6 ± 25.4
Placebo group (N=11)	40.9 ± 20.2	38.2 ± 16.0
P value	0.19	0.10

Table 10 shows the mean improvement in millimetres in Visual analog scale according to parents and child at 36-48 hours was more in montelukast group compared to placebo group but this difference is not statistically significant.. These findings are represented below.

Figure 7. Improvement in Visual analog scale from baseline to 36 - 48 hours assessed by parent and child

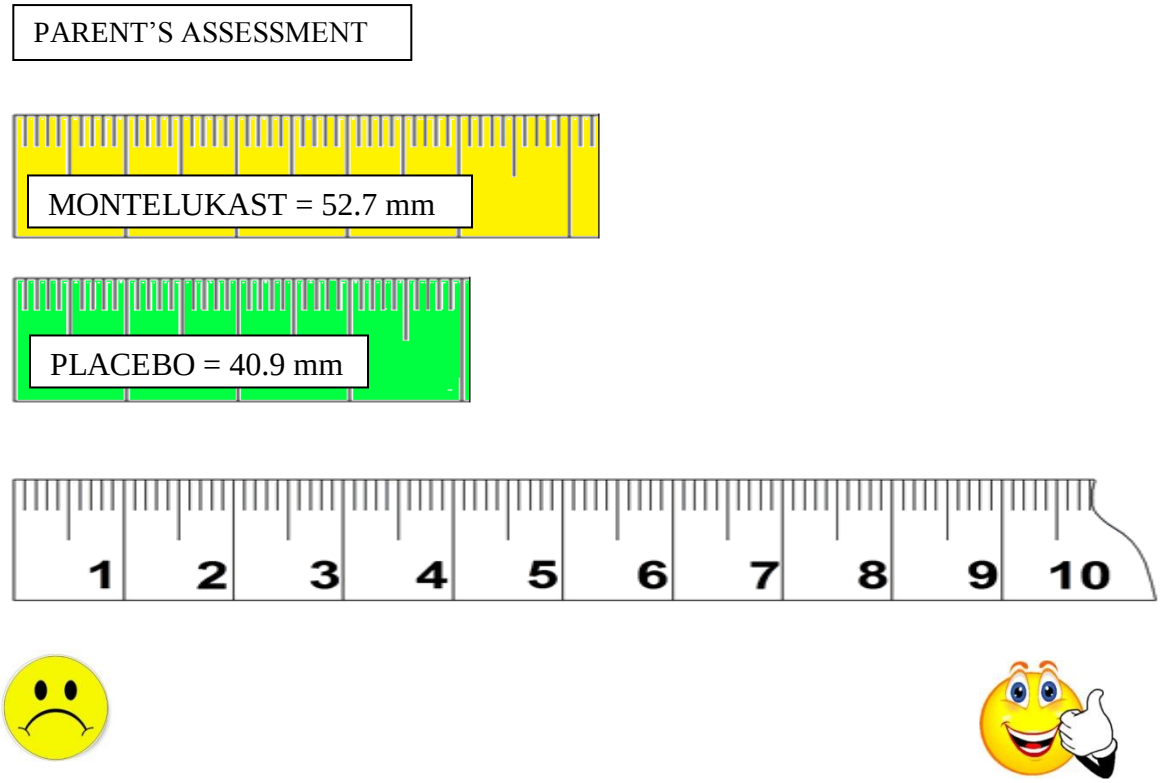


Figure 7 shows the mean improvement in millimetres in Visual analog scale according to parents and child at 36-48 hours was more in montelukast group compared to placebo group.

3. Comparison of reduction in MPIS score at 36-48 hours from baseline

Table 11. Comparison of mean MPIS score reduction at 36-48 hours of drug administration

	MPIS score reduction at 36-48 hours Mean (± SD)	P value
Montelukast group (N=11)	**7.36 ± 2.58**	0.20
Placebo group (N=11)	6.09 ± 1.92	

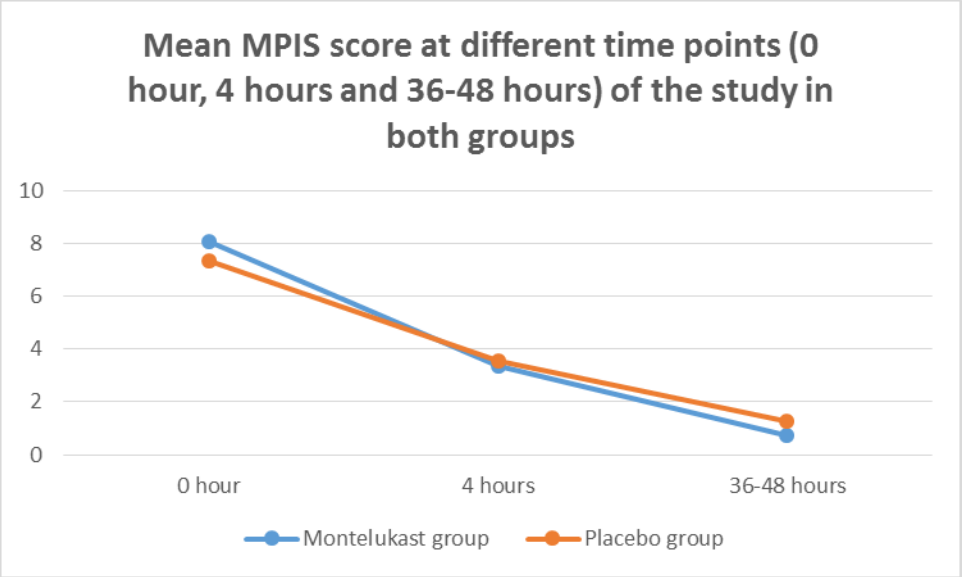
Mean reduction in the score from baseline to 36-48 hours did not show a statistically significant difference between the two groups.

Table 12. Proportion of children who had MPIS score 0-2 at 36-48 hours in both arms

	Children with MPIS score of 0-2 n(%)	Children with MPIS score of >2 n (%)	P value
Montelukast group (N=11)	**11(100%)**	0	0.10
Placebo group (N=11)	**8(72.7%)**	3(27.3%)	

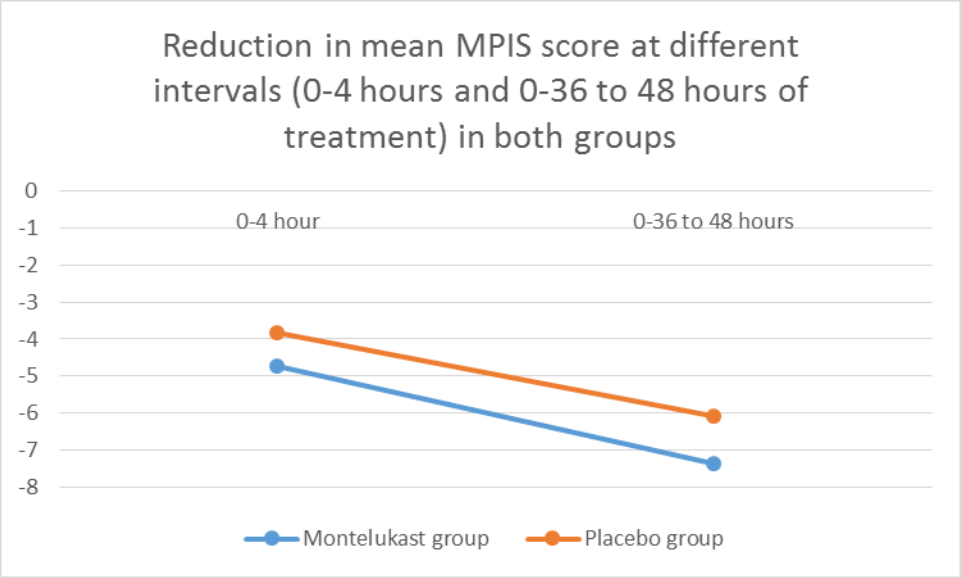
All subjects in the montelukast group had absolute MPIS score below 2 when assessed at 36-48 hours of treatment , which indicated near complete resolution of exacerbation, while 27% in the placebo group still had a score above 2. This difference did not reach statistical significance.

Figure 8. Graphic representation of mean MPIS score at different time points



Baseline mean MPIS score of subjects was more in montelukast arm but at subsequent points of assessment, mean MPIS score in montelukast arm was less compared to placebo. Though statistically significant difference is not demonstrated in the scores between 2 groups, there seems to be a trend towards more rapid improvement in montelukast group.

Figure 9. Graphic representation of change in mean MPIS score at different intervals (0-4 hours and 0-36 to 48 hours) of treatment in both groups



This figure shows reduction in mean MPIS (change is recorded as ***negative value***) in both groups from 0 hour to 4 hours and 0 hour to 36-48 hours. At both points of assessment, drop was more in montelukast arm (reduction of 4.99 in montelukast vs 3.56 in placebo from 0 hour to 4 hours).

4. Comparison of need for steroid use in both arms

Table 13. Comparison of need for steroid use

	Montelukast group n (%)	Placebo group n (%)
Subjects needing steroids	4 (36.4 %)	2 (18%)
Subjects not needing steroids	7 (63.6%)	9 (82%)
Total number of subjects	11 (100%)	11 (100%)

Table 11 shows that systemic steroids were given to 4 patients in the monteleukast group and 2 in the placebo group. Comparison of severity at baseline showed that there were sicker patients in the monteleukast group (more number of hypoxic patients and more patients with moderate severity) necessitating need for steroids. This was clear when we looked at when the decision to give steroids was made. In the montelukast group two subjects were prescribed steroids at baseline in view of the severity. But after 4 hours of initiation of standard asthma care and study drug administration, equal number (2 patients) in each arm needed systemic steroids as shown in table below.

Table 14. Timing of systemic steroid administration

	Montelukast group n(%)	Placebo group n (%)
Within first 4 hours of treatment	2 (18%)	0 (0%)
After 4 hours of treatment	**2 (18%)**	**2 (18%)**
Steroids not used	7 (64%)	9 (78%)
Total	11 (100%)	11 (100%)

In the monteleukast group, two subjects were given steroids at baseline in view of the severity. After 4 hours of treatment, 2 patients in each arm needed oral steroids.

Table 15. Adverse drug reactions observed during the study

Adverse drug reaction	Montelukast group n (%)	Placebo group n (%)
Headache	1 (9%)	-
Vomiting	1 (9%)	-
Urticaria	-	1 (9%)
No adverse events	9 (82%)	10 (91%)
Total number of subjects	11 (100%)	11 (100%)

Table 15 shows the safety profile in both the arms.

In the treatment group, one child developed one episode of vomiting 5 hours after the first dose of montelukast that settled without any medical intervention while another child developed headache after 1 hour of administration of montelukast that responded to one dose of paracetamol.

A child developed mild urticaria after 3 hours of administration of placebo that resolved with anti-histaminic syrup.

Children who developed headache and urticaria were not administered the second dose of study drug, which was to be given 24 hours later as per protocol. However data on these two subjects were included in the intention to treat analysis.

Discussion

Aim of this study was to answer the research question "Is monteleukast - a leukotriene receptor antagonist, useful in acute asthma management in children when the exacerbation is mild to moderate in nature". Randomised double blind placebo controlled trial is the most appropriate design to answer this question.

Interim analysis of this study does not have adequate power to answer the research question. However certain trends have been noted in the results discussed. A similar study done by Nelson et al.(84) was concluded after interim analysis when 26 subjects were enrolled, as statistical predictions showed that completing the proposed sample size is unlikely to give additional information.

Modified pulmonary index score reduction of $\geq$ 4, was set as the primary outcome of our study. MPIS score was also used by Todi et al.(85) in their study where monteleukast was used in moderate to severe exacerbations of asthma. While they considered reduction in absolute score to below 9 as their target, we used a reduction of 4 units in the score as the target. We believe this allows for uniformity in measuring the improvement irrespective of the baseline score.

FEV1/FVC and FEV1 percentage of predicted are the best available measures of bronchial obstruction in clinical pulmonology. Best assessment of bronchodilation

will be by demonstration of FEV1 improvement following treatment. Few studies have used improvement of this parameter as the primary outcome while studying various interventions for acute asthma in adults and children(94). It is well known that spirometry interpretation in children should take into account the aspect of how well the child cooperated with the technique.(95) Results are effort dependent, especially in a sick child. Hence we did not use this as a primary out come in our study. In a similar study Nelson et al.(84) used FEV1 at 3 hours after monteleukast and failed to demonstrate statistically significant improvement.

Peak expiratory flow is also effort dependent and is not the ideal test to assess airflow in emergency situation.(57,96) We used percentage improvement in PEFR after treatment only as a secondary outcome measure and did not find significant difference in the 2 groups. However it is interesting to note that percentage improvement of PEFR at 4 hours was higher in the montelukast arm. Only at final analysis we can clarify if this due to effect of montelukast.

We decided to use visual analogue scale in our study as measurement of subjective improvement as assessed by parent and child .We believe that child returning to school and caretaker reporting back to work will depend on their subjective assessment how well thechild has recovered. The mean improvement (in millimetres) in visual analogue scale by both child and parents at 4 hours and 36-48 hours was more in montelukast group compared to placebo group, however this

difference was not statistically significant. Use of this tool in asthma is described in literature and has been shown to be correlating with other objective markers like FEV1.(90–92) We found VAS a simple tool to use and its utility in asthma research in children is to be investigated.

No serious adverse effects were observed in the study at this point with oral montelukast. We used a higher dose of the drug than routinely recommended for daily treatment as preventer. This was based on observation that higher doses of oral leukotriene receptor antagonists(montelukast 100 and 250 mg and zafirlukast 160 mg) compared to standard doses in adults showed encouraging and positive results(97,98) .Use of higher dosage and longer duration was also suggested by Todi et.al.(85) at the end of their study where one dose of regular monteleukast dose was used in moderate to severe exacerbations in childeren.

Our study differs from a study done by Todi.et.al(85) as we included children with mild to moderate acute exacerbations and excluded those with severe exacerbations. While all the children in the study by Todi et al(85) received systemic steroids at the beginning of the study, we did not routinely administer steroids to all. Systemic steroid is a potent anti-inflammatory agent and the effect of monteleukast in acute asthma is unlikely to be revealed when steroids are administered concurrently. Since it is not ethical to withhold systemic steroids in acute asthma, we allowed children who needed steroids to remain in the study.

Analysis of our data showed that only 2 children had received steroids before 4 hour mark at which point primary outcome was assessed. It will be interesting to do a subgroup analysis of subjects (at the final conclusion of study) who did not receive steroids by 4 hours to document the improvement which is exclusively attributable to monteleukast.

Children with moderate or severe acute exacerbations may have a rapid onset of improvement and sustained effect after receiving intravenous montelukast. This was the observation in adults as reported by Camargo and Dockhorn in separate studies(87,88,99). There was a trend towards greater efficacy with IV formulations even though the plasma AUC levels were similar to oral montelukast in the study by Dockhorn(87) . Intravenous monteleukast is not routinely used in children and could be the subject of future research.

In summary ,interim analysis of a small sample of subjects included in this randomised double blinded study did not show statistically significant difference between monteleukast and placebo in the parameters assessed namely MPIS, peak expiratory flow rate, visual analog scale at 4 hours and after 36 hours.

Strengths of the study

1. Recommended steps in the planning, trial registration and execution of a randomized controlled study were strictly followed.

2. The primary outcome was measured using MPIS score that has predominantly objective components. As parameters were assessed at all points by the same investigator (who was blinded), there is minimal influence on this score by the subjective components (viz. accessory muscle use and I: E ratio).

3. As primary outcome was measured at four hours, deviation from protocol that happened in the case of 2 patients (after four hours) did not affect the assessment of primary outcome.

4. Pharmaceutical companies did not have any role in the conduct of the study or analysis.

Limitations

1. Our study did not achieve target sample size as planned, and we have given an interim analysis report. Though it was planned to recruit the required number over one year we faced following difficulties:

a) Drug and placebo preparation and quality assessment of the preparation led to time delay.
b) Asthma exacerbations are predominantly seen in the cooler months of the year. Due to delay in administrative clearing of the proposal as well as other difficulties mentioned above, we were not able to recruit patients during most of winter 2014.

However, we propose to continue patient recruitment till February 2016 and hope to achieve the required sample size.

2. Some patients could not be called back to record personal best PEFR as they were from distant places.
3. At this point of analysis, there are sicker patients allotted to monteleukast group which resulted in more systemic steroid use. This might have affected the outcomes measured. We hope randomization would equate the differences by the time, target sample size is reached.

Conclusion

1. Interim analysis of data from a small sample of 22 subjects included in this randomised double blinded study did not show statistically significant difference between monteleukast and placebo in the parameters assessed namely MPIS, peak expiratory flow rate, visual analog scale at 4 hours and 36 to 48 hours when the study drug was combined with standard treatment of mild to moderate exacerbation of asthma in children.

2. Monteleukast group showed a trend towards better outcome in all parameters assessed.

3. Visual analog scale as an outcome measurement shows some promising results even at this interim analysis stage.

4. There were no significant adverse events associated with the use of montelukast in higher than standard dosage.

Recommendations

Larger clinical trials with adequate sample size are needed to ascertain the role of montelukast in acute asthma exacerbations in children.

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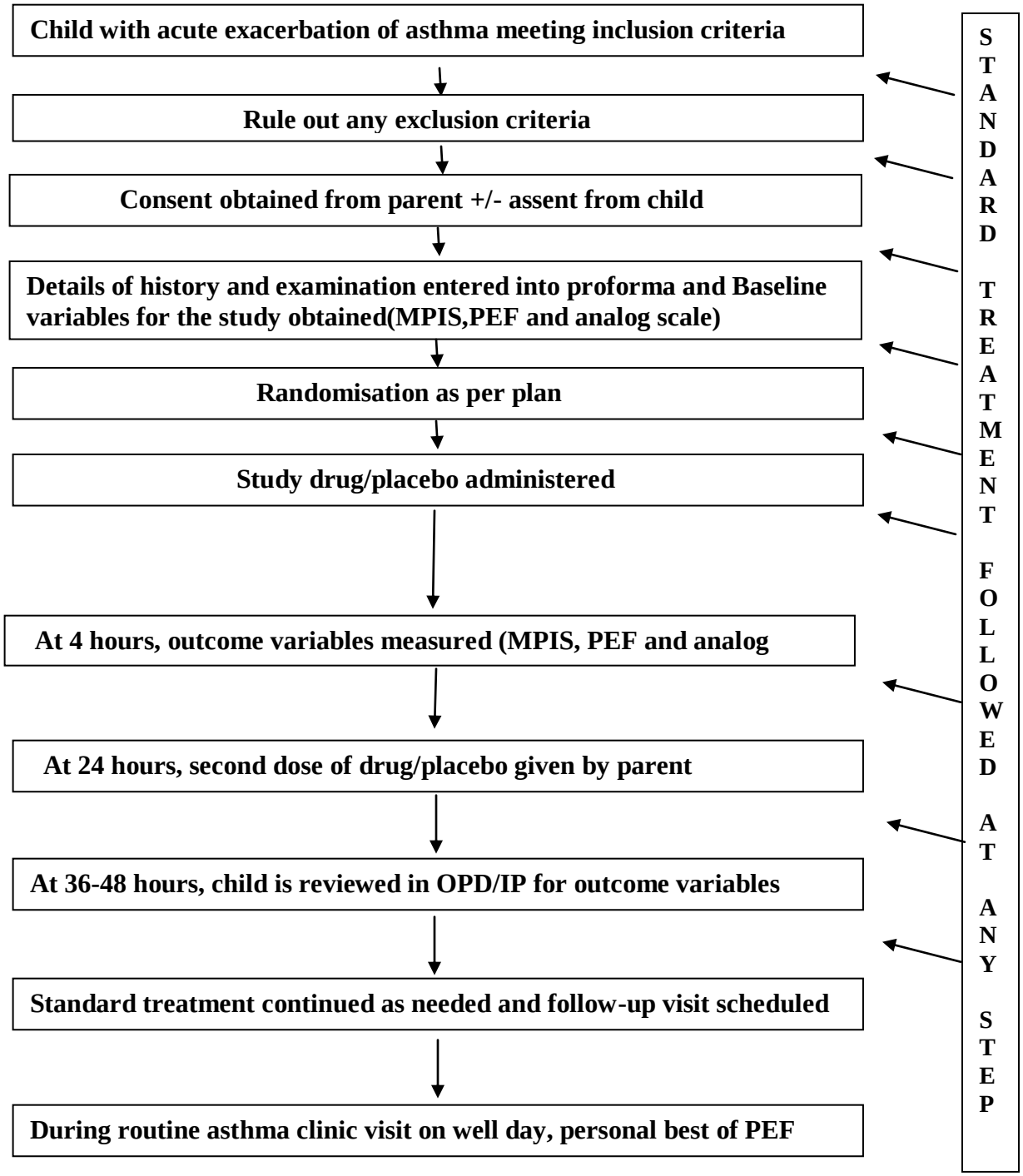
APPENDIX

APPENDIX (I) STUDY PROTOCOL



APPENDIX. (II) ENGLISH INFORMATION SHEET AND CONSENT FORM

Information sheet

You are being requested to participate in a study done to look at the benefit of a drug called montelukast in acute attacks of asthma in children of 5 to 15 years age group.

Asthma is one of the most common long-term diseases of children. Asthma is a disease that affects the lungs. Asthma causes repeated episodes of wheezing, breathlessness, chest tightness, and night time or early morning coughing. If your child has asthma, he or she will have asthma attacks only when something bothers his or her lungs like virus infections, dust, smoke etc. Despite a great deal of research, the cause of asthma is still unknown. *Asthma can be controlled* by knowing the warning signs of an attack, staying away from things that trigger an attack, and following the advice of a doctor for prevention of attacks.

There are two different types of asthma medications used in the treatment of asthma.

1.Reliever medications: relax the smooth airway muscles and help them re-open

2.Preventer medications: reduce inflammation

Reliever medications make breathing easier but don't have any long-term preventive action. They work by relaxing the small muscles surrounding the narrowed airways allowing them to re-open. The effect is usually quick and noticeable but short acting. Examples of reliever medications are salbutamol,levosalbutamol etc.

Preventer medications work by preventing them from becoming swollen, and decreasing the amount of mucus. They also reduce the sensitivity of the airways to trigger factors. In this way, they prevent and decrease the severity of attacks. Preventer medications take time to reach their full effect. They should be taken every day, whether there are symptoms or not. They usually do not relieve an acute asthma attack.

Current practice of acute attack is treatment with salbutamol (reliever medication) by nebulisations or metered dose inhalers, along with oral or injectable steroids (in some cases).

Montelukast is a preventer medication which is taken orally once a day in tablet form and is used routinely in children with asthma and nose allergy.. Side effects are uncommon and mild, such as headache and abdominal pain, but are very rare.

There have been studies in adults showing usefulness of montelukast in acute asthma and very few in young children showing benefit. Research is being under taken to look at possible role of montelukast in acute attacks of asthma. It seems to us, that among our population, montelukast may be a useful and good drug for mild to moderate attacks of acute asthma. Hence we are doing this study to see the role of montelukast in acute attacks of asthma in the age group 5-15 years. If this is indeed proved, the information may help to treat these children differently in future .

If you take part what will you have to do?

If you agree to participate in the study , your child will be treated for his/her acute attack of asthma in the ward/casualty as the child's clinical condition needs with standard treatment using nebulisations +/- steroids. In addition, your child will receive either montelukast or a placebo (which is a drug with no clinical effect) in the beginning and 24 hours later. Your child has an equal chance of being in the monteleukast or placebo group. Child will be monitored carefully for improvement till 48 hours. For the first 4 hours child will be observed in the hospital.After that child may be discharged home or kept for further observation in casualty/ ward as per the condition of the child. If his / her clinical condition improves he will be discharged home anytime after 4 hours and you can bring him/her again for a visit to the hospital the next day (after 36 hours). You can continue asthma treatment at home using inhalers.

As a part of the study we will measure improvement of your child using peak flow meter. This is a simple device into which the child is asked to blow. It is not painful and easy to do for children. Another way in which we measure improvement is to ask you and the child to mark on line with pictures how well the child feels after treatment.This is called visual analog scale.This is also a simple method which the child can easily understand and mark on a line with pictures. There are no blood tests or any painful procedures as part of the study. You do not have to make any payment for these 2 tests.At the end of the study, we will analyse the data obtained from all children included in the study to see if there is difference in the rate of improvement between the 2 groups (monteleukast vs placebo).

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your child's/ward's usual treatment at this hospital in any way.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but your child/ward will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study. The data will be stored in a secure and confidential location in office of child health unit-3.

Informed Consent form to participate in a research study

Study Title: Monteleukast for acute asthma exacerbation in children 5years -15 years-_A randomized placebo controlled study
Study Number: ___

Subject's Initials: _____ Subject's Name: _____
Date of Birth: _____ Age: _____

(Please tick boxes)
(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]
(ii) I understand that participation of my child/ward in the study is voluntary and that he is
free to withdraw at any time, without giving any reason, without his medical care or legal rights being affected. [ ]
(iii) I understand that the doctors, the Ethics Committee and the regulatory authorities will not need my permission to look at his health records both in respect of the current study and any further research that may be conducted in relation to it, even if he withdraw from the trial. I agree to this access. However, I understand that identity will not be revealed in any information released to third parties or published. [ ]
(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]
(v) I voluntarily agree for my child's /ward's participation in the above study. [ ]

Signature (or Thumb impression) of legally representative person/parent:
Relation to child: _____
Date: _____/_____/_____
Signatory's Name: _____

Signature of the Investigator: _____
Date: _____/_____/_____
Study Investigator's Name: _____

APPENDIX (III). TAMIL INFORMATION SHEET AND CONSENT FORM

தகவல் கையேடு

ஆய்வு: 5 முதல் 15 வயது வரை உள்ள சிறுவர்களுக்கு ஏற்படும் கடுமையான ஆஸ்துமா தாக்குதலை கையாள 'மான்டேலுகாஸ்ட்' என்ற மருந்து பயன்படுத்துவதன் பயனை கணிக்கும் ஆய்வு.

5 முதல் 15 வயது வரை உள்ள சிறுவர்களுக்கு ஏற்படும் கடுமையான ஆஸ்துமா தாக்குதலை கையாள 'மான்டேலுகாஸ்ட்' என்ற மருந்து பயன்படுத்துவதன் பயனை கணிக்கும் ஒரு ஆய்வில் தங்கள் குழந்தையை பங்குகொள்ளச் செய்ய கேட்டுக்கொள்ளப்படுகிறீர்கள்.

சிறுவர்களை நீண்ட காலம் தாக்கி வரும் மிக பிரபலமான நோய் ஆஸ்துமாவாகும். ஆஸ்துமான நுறையீரலை தாக்கும் நோயாகும். மூச்சுகஷ்டம், மார்பு பகுதியில் அழுத்தம் மற்றும் இரவு அல்லது விடியற்காலையில் இருமல் போன்றவை ஏற்படும். உங்கள் பிள்ளைக்கு ஆஸ்துமா நோய் இருந்தால் புகை, தூசி, கிருமிகள் போன்றவற்றின் தாக்குதல்கள் இருந்தால் மட்டுமே நோயின் அறிகுறிகள் வெளிப்படுகின்றன. அதிக அளவிலான ஆராய்ச்சிகள் நிறைவேறியும் ஆஸ்துமாவின் காரணம் கண்டுபிடிக்கப்படவில்லை. இந்நோயின் தாக்குதலுக்கு முன் ஏற்படுமட் அறிகுறிகளை அறிந்து அவற்றை தவிர்த்து மருத்துவரின் அறிவுரையை பின்பற்றுவதால் நோயின் தாக்கத்தை கட்டுப்படுத்தலாம்.

ஆஸ்துமா நோய்க்கு சிகிச்சை அளிக்க இருவிதமான மருந்துகள் பயன்படுத்தப்படுகின்றன.

1. விடுவிப்பு மருந்துகள்: சுவாசக்குழாய் தசைகளின் இறுக்கத்தை விடுவித்து மீண்டும் திறக்கச்செய்தல்.
2. தடுப்பு மருந்துகள்: தாக்குதலை குறைத்தல்.

விடுவிக்கும் மருந்துகள் மூச்சு எடுப்பதை இலகுவாக்குவதே தவிர, நீண்ட கால தடுப்பு முறைகளை கையாள்வதில்லை. சுவாசக்குழாய்களை சுற்றியுள்ள தசைகளின் இறுக்க நிலையை குறைய செய்து மீண்டும் திறக்க செய்கின்றன. உடனடியாக விடிவு வெளிப்படையாக ஏற்பட்டாலும் தற்காலிகமாகவே உள்ளது. சால்பூடமால் மற்றும் லெவொ சால்பூடமால் போன்றவை இதற்கு உதாரணங்களாகும்.

தடுப்பு மருந்து வகைகள் சுவாசக் குழாய்கள் வீங்காமல் சளி சுரப்பதை தடுக்கவும் உதவுகின்றன. சுவாசக் குழாய்களின் உணர்வு திறனையும் இவை குறைக்கின்றன. இவ்வழியாய் நோயின் தாக்கம் வெகு அளவு குறைக்கப்படுகிறது. தடுப்பு மருந்துகள் முழு வீச்சாய் செயல்பட நேரம் எடுக்கின்றன. நோயின் அறிகுறிகள் இருந்தாலோ இல்லாமலிருந்தொலோ ஒவ்வொரு நாளும் இம்மருந்து எடுக்கப்படவேண்டும். பொதுவாக இம்மருந்துகள்ன கடுமையாக தாக்கும் நோயை உடனடியாக குணப்படுத்த அதிக அளவில் உதவுவதில்லை. தற்போது கடுமையாக நோய் தாக்கும் போது சால்பூடமால் (விடுவிப்பு மருந்து) பயன்படுத்தி அல்லது அளவோடு சுவாச மருந்துகள் மற்றம் ஆவி பிடித்தல் போன்றவை கையாளப்படுகிறது. சில சமயங்களில் ஸ்டிராய்டுகள் வாய்மூலமாக அல்லது ஊசி மூலமாகவும் கொடுக்கப்படுகிறது.

மான்டேலூகாஸ்ட் என்ற மருந்து தடுப்பு வகையானது. வாய் வழியாய் ஒரு நாளுக்கு ஒன்று என்று மாத்திரையாக கொடுக்கப்படுகிறது.. தூண்டப்படும் வகையான ஆஸ்துமா நோயையுடைய சிறுவர்களுக்கு இது கொடுக்கக்படுவதோடு ஒவ்வாமை (அலர்ஜி) வகையான சளி பிடிக்கும் பிள்ளைகளுக்கும் பயன்படுத்தப்படுகிறது. எப்போதாவது சில சமயங்களில் மட்டும் தலைவிலி மற்றும் வயிற்றுவலி போன்ற பக்க விளைவுகள் வருவதுண்டு.

ஒரு சில சிருவர்களிலும் பெரியவர்களிடையேயும் மாண்டேலூகாஸ்ட் கடுமையான நோய் தாக்குதலுக்கு பயன்படுத்தப்படுகிறது. குழந்தைகளின் கடுமையான நோய் தாக்குதலின் சிகிச்சைக்கு மான்டேலூகாஸ்டின் பயன் குறித்து ஆராய்ச்சி செய்யப்பட்டு வருகிறது.

நம்முடைய சமுதாயத்தில் மாண்டேலூகாஸ்ட் கடுமையான ஆஸ்துமா தாக்குதலை கட்டுப்படுத்த பயனுள்ளதாக இருக்கும் என்று நாங்கள் எண்ணுகிறோம். 5 – 15 வயதுள்ள ஆஸ்துமா நோயாளிகளிடையே இந்த ஆய்வை செய்து வருகிறோம். இது நிருபிக்கப்படுமேயானால் எதிர்காலத்தில் இவ்வகையான சிறுவர்களுக்கு வித்தியாசமான சிகிச்சை அளிக்க வாய்ப்புண்டு.

நீங்கள் பங்கேற்றால் என்ன செய்ய வேண்டும்?
நீங்கள் இந்த தகவலறிக்கை மற்றும் ஒப்புதல் அறிக்கையை படித்து \ படிக்கப்பட்டு புரிந்து கொண்டு இந்த ஆய்வில் உங்கள் குழந்தையை பங்கு கொள்ள சம்மதித்தால் உங்கள் பிள்ளைக்கு கடுமையான தாக்குதல் வரும் போது சாதாரண சிகிச்சை பிரிவு அல்லது அவசர சிகிச்சை பிரிவில் வழக்கமாக அளிக்கப்படும் ஆவி பிடித்தல் (nebulisation)+/- ஸ்டிராய்டு சிகிச்சை அளிக்கப்படும். இதனுடன் மான்டேலூகாஸ்ட் அல்லது ஒரு விளைவையும் ஏற்படுத்தாத வெற்று மருந்து (பிலாசிபோ) அளிக்கப்படும். உங்கள் குழந்தை இரண்டு குழுக்களில் ஏதாவது ஒரு குழுவில் இடம் பெற வாய்ப்புள்ளது. குழந்தை 48 மணி நேரம் வரை உடல் நிலை முன்னேற்றத்திற்காக கவனமாக கண்காணிக்கப்படும். முதல் 4 மணி நேரத்திற்கு மருத்துவமனையில் கண்காணிக்கப்படுவர், அதன் பிறகு குழந்தையின் உடல் நிலையை பொறுத்து டிஸ்சார்ஜ் செய்யப்படுவர் அல்லது அவசர பிரிவில அல்லது வார்டில் கண்காணிக்கப்படுவார்.
குழந்தையின் உடல் நிலை முன்னேற்றமடைந்தால் 4 மணி நேரத்திற்கு பிறகு எப்பொழுதிலும் டிஸ்சார்ஜ் செய்யபடலாம் மற்றும் நீங்கள் குழந்தையை மறுநாள் (36 மணி நேரத்திற்கு பிறகு) மருத்துவமனைக்கு மீண்டும் பரிசோதிக்க அழைத்து வரலாம். நீங்கள் ஆஸ்துமாவிற்கு சிகிச்சையை வீட்டிலேயே இன்ஹேலர்களை பயன்படுத்தி தொடரலாம்.

ஆய்வின் ஒரு பகுதியாக நாங்கள் குழந்தையின் உடல் நிலை முன்னேற்றத்தை ஒரு மீட்டர் கொண்டு அளவிடுகிறோம். இது ஒரு எளிய சாதனம், குழந்தையை இதனூடே ஊதச்சொல்லுவோம். இது வலி ஏற்படுத்தக்கூடியதல்ல மற்றும் குழந்தைகளுக்கு செய்வதற்கு எளிதானது. மற்றோரு முறை உங்களையும் குழந்தையையும், படங்களிலும் கோடுகளிலும், குழந்தையின் உடல் நிலை முன்னேற்றத்தை சிகிச்சைக்கு பிறகு எவ்வாறு உணர்கிறீர்கள் என்று குறிக்கச்சொல்வது. இது படங்களை கொண்டு ஒப்புமை செய்யும் முறை எனப்படும். இதுவும் மிக எளிய முறையாகும். குழந்தைகள் படங்களை பார்த்து கோடுகளில் குறிக்கமுடியும். இதில் எந்த இரத்தப்பரிசோதனையோ வலி தரக்கூடிய செயல்முறைகளோ இல்லை. இந்த பரிசோதனைகளுக்கு நீங்கள் எந்த கட்டணமும் கட்டத்தேவையில்லை.

இந்த ஆய்வு செய்யப்படும் காலத்தில் உங்கள் குழந்தைக்கு அளிக்கப்படும் மற்ற சிகிச்சைமுறைகளில் எந்த மாற்றமும் ஏற்படாது. நீங்கள் இந்த ஆய்வில் பங்குகொள்ள சம்மதிக்காவிட்டாலும் உங்கள் குழந்தைக்கு அளிக்கப்படும் சிகிச்சையில் எந்த மாற்றமும் இருக்காது.

இந்த ஆய்விலிருந்து ஆய்வு தொடங்கிய பின் விலகிக்கொள்ளலாமா?
ஆய்வில் பங்கேற்பது உங்கள் தன்னிச்சையான முடிவு. நீங்கள் ஆய்வில் பங்கேற்க அளித்த அனுமதியை திரும்பப்பெற சுதந்திரமாக முடிவுசெய்யலாம். நீங்கள் அவ்வாறு முடிவெடுத்தால் அது இந்த மருத்துவமனையில் அளிக்கப்படும் வழக்கமான சிகிச்சையை எந்த விதத்திலும் பாதிக்காது.

உங்கள் தனிப்பட்ட விவரங்கள் இரகசியமாக வைக்கப்படுமா?
உங்கள் குழந்தையை பற்றி இந்த ஆய்வின் போது பெறப்படும் தகவல்கள் அனைத்தும் பாதுகாப்பாக இரகசியமாக வைக்கப்படும். உங்கள் குழந்தை இந்த ஆய்வின் பதிவுகளில் ஒரு இரகசிய குறியீட்டெண்ணால் அறியப்படும். ஆய்விலிருந்து பெறப்படும் முடிவுகள் மருத்துவ இதழில் பிரசுரிக்கப்படும்போதோ மாநாட்டில் விவாதிக்கப்படும் போதோ உங்கள் குழந்தையைப்பற்றிய தகவல்களை அடையாளம் காண முடியாது. இந்த தகவல்கள் அனைத்தும் இரகசியமாக, பத்திரமாக குழந்தைகள் நல பிரிவு – 3 அலுவலகத்தில் பாதுகாக்கப்படும்.

உங்களுக்கு மேலும் இந்த ஆய்வு பற்றி கேள்விகள் இருந்தால் கீழ்கண்ட மருத்துவரை அணுகவும்

டாக்டர் ராகுல் ரெட்டி.
குழந்தைகள் பிரிவு
கிருத்துவ மருத்துவ கல்லூரி
வேலூர் – 632 004

ஒப்புதல் அறிக்கை

ஆய்வு: 5 முதல் 15 வயது வரை உள்ள சிறுவர்களுக்கு ஏற்படும் கடுமையான ஆஸ்துமா தாக்குதலை கையாள 'மான்டேலுகாஸ்ட்' என்ற மருந்து பயன்படுத்துவதன் பயனை கணிக்கும் ஆய்வு.

ஆய்வு எண்: குழந்தையின் மருத்துவ பதிவேடு எண்

குழந்தையின் பெயர்: தாயின் மருத்துவ பதிவேடு எண்

பிறந்த தேதி

1. நான் இந்த ஆராய்ச்சியின் தகவல் அறிக்கையை படித்து\ எனக்காக படிக்கப்பட்டு புரிந்துகொண்டேன் என்று உறுதியளிக்கின்றேன். மேலும், இந்த ஆராய்ச்சி பற்றி என் சந்தேகங்கள் நிவர்த்தி செய்யப்பட்டது என்றும் உறுதியளிக்கின்றேன. ☐

2. இந்த ஆராய்ச்சியில் என் குழந்தையை பங்கு கொள்ள செய்வது என் தன்னிச்சையான முடிவு என்றும் இந்த ஆராய்ச்சியிலிருந்து எப்பொழுது வேண்டுமானாலும் எந்த காரணமுமில்லாமல் விடுவித்துகொள்ளலாம் என்றும் அது என் குழந்தைக்கு அளிக்கப்படும் மருத்துவ சிகிச்சையையும் எங்களது சட்டபூர்வமான உரிமையையும் எந்த விதத்திலும் பாதிக்காது என புரிந்துகொண்டேன் என்று உறுதியளிக்கின்றேன். ☐

3. இந்த ஆய்வின் ஆதரவாளர்கள் மற்றும் அவர் சார்பாக வேலை செய்பவர்கள், நெறிமுறைகள் குழு மற்றும் கட்டுப்பாட்டு அதிகாரிகள் என் குழந்தையின் மருத்துவ பதிவேடுகளை என் குழந்தை இந்த ஆய்விலிருந்து விலகிக்கொண்டாலும் பார்க்கலாம் என்று புரிந்து கொண்டேன். இதற்கு நான் ஒப்புதல் அளிக்கின்றேன். என் குழந்தையை பற்றிய எந்த தகவலும் முன்றாவது நபருக்கு தெரியப்படுத்தப்படாது என்றும் பிரசுரிக்கபடாது என்றும் புரிந்து கொண்டேன். ☐

4. இந்த ஆய்விலிருந்து பெறப்படும் எந்த தகவல்களையும் முடிவுகளையும் அறிவியல் நோக்கத்திற்கு பயன்படுத்த நான் தடையாக இருக்க மாட்டேன் எனவும் உறுதியளிக்கின்றேன் ☐

5. இந்த ஆய்வில் என் குழந்தையை பங்கு கொள்ள செய்ய தன்னிச்சையாக ஒப்புதல் அளிக்கின்றேன். ☐

6. எனது குழந்தையின் பரிசோதனை முடிவுகளை இந்த ஆய்விற்கு பயன்படுத்திக்கொள்ள அனுமதியளிக்கின்றேன. ☐

பெற்றோரின் கையொப்பம் மருத்துவரின் கையொப்பம்

பெயர்

தேதி:

சாட்சியின் கையொப்பம் உறவுமுறை

தேதி

APPENDIX (IV): STUDY PROFORMA / CLINICAL RESEARCH FORM

Study No.: **Study drug No.:**

Demographics:

Name: Hosp No:
Age: Date of birth:
Sex:
Address:

Weight: Height:
Phone I: Phone2:

INCLUSION CRITERIA		**EXCLUSION CRITERIA**	
Age 5-15 years	Yes / No	Severe exacerbation	Yes / No
Baseline score 5-11	Yes / No	On oral steroids for current symptoms	Yes / No
Consent obtained	Yes / No	On monteleukast as preventer	Yes / No
Can come for follow up	Yes / No		

Modified Pulmonary index score /PEF at observation points:

	Reference for scoring	Base line	4 hrs	36-48 hrs
	Date & Time →			
SaO2 at room air	***O*****=**>95% / 1=93%-95% / ***2*****=**90%-92% / 3=<90%			
Accessory muscle use	***0*****=**none /1= mild /2= moderate /3-=severe			
Inhalational/exhalation ratio	0=2:1 /***1*****=**1:1 /***2*****=** 1:2 /***3*****-**=2:3			
Wheezing	***0*****-**None / 1-End expiratory / 2-Inspi & expi /3- Inspi & expi, decreased aeration			
Heart rate (beats/min)	***0*****-**<100 / 1-100–120 / 2-121–140 / 3->140			
Respiratory rate (per min)	<6 Years 0- 30 / 1-31–45 / 2-46– 60 / 3->60 >6 Years ***0*****-** <20 / ***1*****-**21–35 /***2*****-** 36–50 /***3*****-** >50			
Modified pulmonary index score				
PEF				
Analog scale rating (from 0 – 10 on breathlessness perception)				

Best measured PEF:

HISTORY

Onset of asthma symptoms (age):

Duration of current exacerbation :

Preceded by URTI - Yes / No

On inhaled steroids – Yes/ No Name: Dose

History of allergic rhinitis–Yes / No

Family history of asthma- Yes / No

Time of 1st dose of study drug –

Time of 2nd dose of study drug -

FOLLOWUP INFORMATION

Oxygen given: Yes/ No Duration:

IV fluids : Yes /No

Antibiotics: Yes/No Name: oral steroids:

Total No. of Salbutamol : nebulisation taken MDI use

Total No. of Ipravent : nebulisation taken MDI use

Side effects

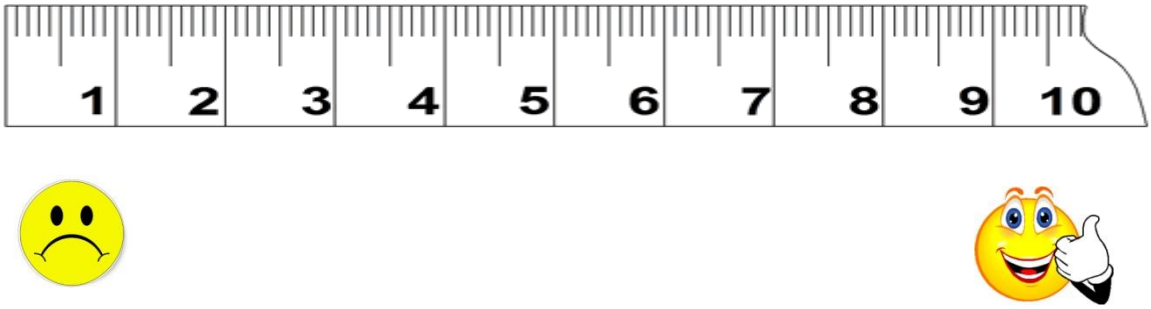
Headache : Yes/ No Abd pain: Yes/No

Dizziness: Yes/No Diarrhoea: Yes/No Others:

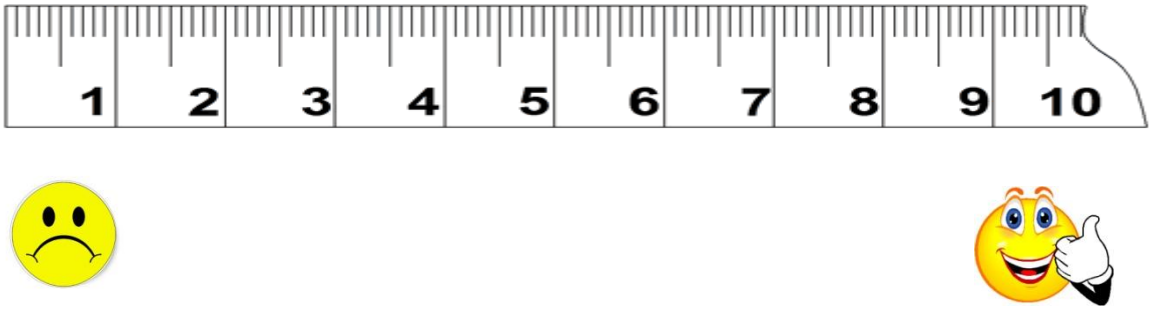
Visual analog score at observation points:

1.<u>Perception of parent:</u>

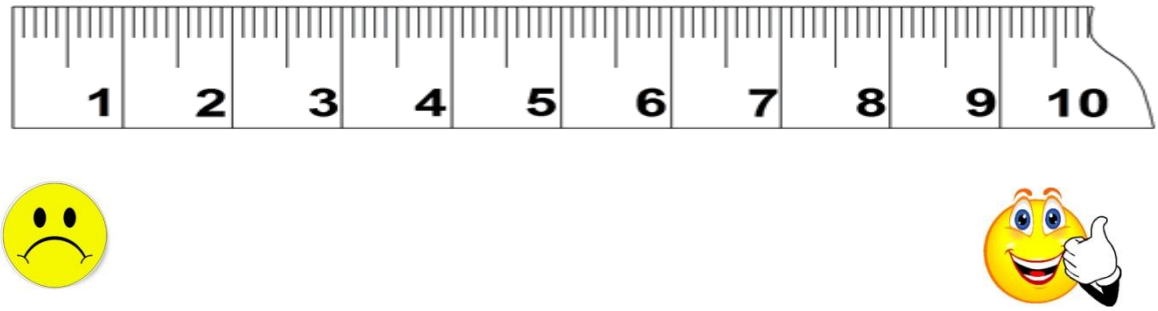
Baseline



4 hr

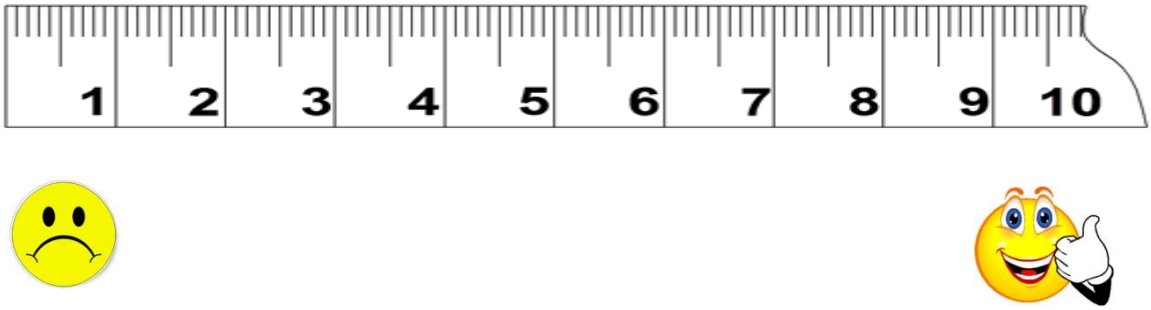


36 – 48 hrs

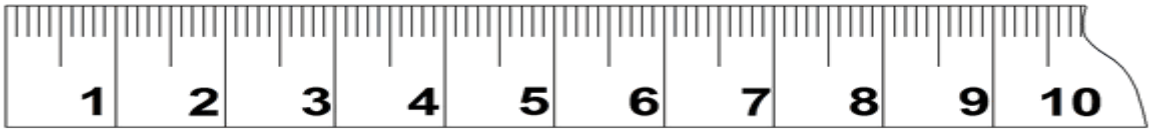


2.<u>Perception of child:</u>

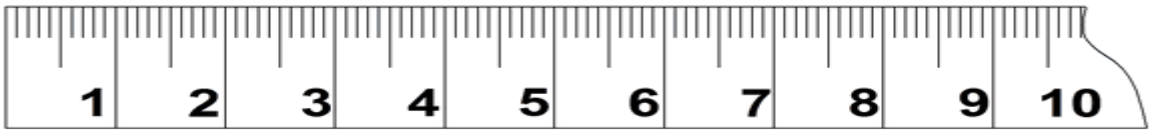
Baseline



4 hr



36 – 48 hrs



Monitoring sheet for parents		
Date and Time	**Treatment taken**	
	Nebulisations	**Asthalin MDI**

APPENDIX (V): CTRI REGISTRATION FOR

Clinical Trial Details (PDF Generation Date :- Fri, 18 Sep 2015 09:20:05 GMT)

CTRI Number	CTRI/2015/01/005423 [Registered on: 19/01/2015] - **Trial Registered Prospectively**
Last Modified On	15/01/2015
Post Graduate Thesis	Yes
Type of Trial	Interventional
Type of Study	Drug
Study Design	Randomized, Parallel Group, Placebo Controlled Trial
Public Title of Study	usefulness of Monteleukast in acute asthma in children
Scientific Title of Study	Monteleukast for acute asthma exacerbation in children 5years -15 years- A randomized double blind placebo controlled study

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	Dr C Rahul Reddy
Designation	Post graduate, Department of Paediatrics
Affiliation	Christian Medical College, Vellore
Address	Paediatrics unit 3, CMC hospital,Vellore Vellore TAMIL NADU 632001 India
Phone	9003213730
Fax	04162282232054
Email	rahulreddychintala@gmail.com

Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
Name	DrSneha Varkki
Designation	Professor, Department of Paediatrics
Affiliation	Christian Medical College, Vellore
Address	Paediatrics unit 3, CMC hospital,Vellore Vellore TAMIL NADU 632002 India
Phone	09488840434
Fax	04162282232035
Email	snehatitus85@yahoo.com

Details Contact Person (Public Query)

Details Contact Person (Public Query)	
Name	Dr C Rahul Reddy
Designation	Post graduate, Department of Paediatrics
Affiliation	Christian Medical College, Vellore
Address	Paediatrics unit 3, CMC hospital,Vellore Vellore TAMIL NADU 632001 India
Phone	9003213730
Fax	04162282232054
Email	rahulreddychintala@gmail.com

Source of Monetary or Material Support

Source of Monetary or Material Support
> Fluid research Fund,Christian Medical college Vellore

Primary Sponsor

Primary Sponsor Details	
Name	Fluid research FundChristian Medical college
Address	CMC hospital,Vellore-632001
Type of Sponsor	Research institution and hospital

Details of Secondary Sponsor

Name	Address
NIL	NIL

Countries of Recruitment

List of Countries
India

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
DrCRahul Reddy	Christian medical college, Vellore	Paediatric unit 3 ,5th floor ISSC building,Christian medical college,Vellore Vellore TAMIL NADU	09003213730 rahulreddychintala@gmail.com

Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
Ethics committee and Institutional review board,CMC Vellore	Approved	26/11/2014	No

Regulatory Clearance Status from DCGI

Status	Date
Not Applicable	No Date Specified

Health Condition / Problems Studied

Health Type	Condition
Patients	Childhood Asthma

Intervention / Comparator Agent

Type	Name	Details
Intervention	Montelukast in syrup	10mg at 0hr and 24 hr for age below 12 yrs 20mg at 0 hr and 24 hr for age above12 yrs
Comparator Agent	Placebo-syrup base identical in colour,taste and volumeto study drug preparation	given at 0 hr and 24 hr in

Inclusion Criteria

Inclusion Criteria	
Age From	5.00 Year(s)
Age To	15.00 Year(s)
Gender	Both
Details	Children aged 5-15 completed years with a diagnosis of asthma presenting with mild to moderate acute exacerbation (modified pulmonary index score 5-11)

Exclusion Criteria

Exclusion Criteria	
Details	1.Severe exacerbations with a modified pulmonary index score >12. 2.Children who have been already started on oral steroids for present exacerbation 3.Children on treatment with daily monteleukast in the last month 4.Children who cannot remain in hospital for atleast 4 hours from the onset of treatment.

Method of Generating

Computer generated randomization

Random Sequence	
Method of Concealment	Centralized
Blinding/Masking	Participant and Investigator Blinded

Primary Outcome

Outcome	Timepoints
Modified pulmonary index score 4 hours after study drug.Reduction in score will be compared with placebo arm	Modified Pulmonary Index Score(MPIS)measured at 0 hour and 4 hours.

Secondary Outcome

Outcome	Timepoints
need for steroid use	4 hours and 36-49 hours
Improvement in peak expiratory flow rate	from baseline to 4 hours and 36 -48 hours
subjective improvement of symptoms using visual analog scale	from baseline to 4 hours and 36 -48

Target Sample Size	**Total Sample Size**=104 **Sample Size from India**=104
Phase of Trial	N/A
Date of First Enrollment (India)	20/01/2015
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years**=1 **Months**=0 **Days**=0
Recruitment Status of Trial (Global)	Not Applicable
Recruitment Status of Trial (India)	Not Yet Recruiting
Publication Details	
Brief Summary	This placebo controlled double blinded study to assess the effect of monteleukast in mild to moderate acute asthma exacerbation on children 5-15 years will be done in the emergency department and outpatient area of Paediatric department,CMC Hospital,Vellore. After obtaining consent from parents children will be assigned to treatment or placebo arm using block randomization table. Treatment arm will receive monteleukast 10mg for children < 12 years and 20mg for those >12 years ,at 0 hrs and 24 hrs. Assessment of MPIS score,PEF and visual analog score will be done at 0hrs,4 hrs and 36-48 hours. Groups will be compared using intention to treat and per protocol analysis. Primary outcome is reduction in Modified Pulmonary Index Score(MPIS) from baseline to 4 hours after Monteleukast compared to placebo when combined with standard management. Secondary outcomes are 1)need for steroid use, 2)Improvement in peak expiratory flow rate from baseline to 4 hours and 36 -48 hours, 3)subjective improvement of symptoms using from baseline to 4 hours and 36 -48 using visual analog scale

APPENDIX (VI): MODIFIED PULMONARY INDEX SCORE

Table 1. The Modified Pulmonary Index Score

Category	Score			
	0	1	2	3
Oxygen saturation, %	>95	93–95	90–92	<90
Accessory muscle use	None	Mild	Moderate	Severe
Inhalation-exhalation ratio	2:1	1:1	1:2	1:3
Wheezing	None	End expiratory	Inspiratory and expiratory wheeze, good aeration	Inspiratory and expiratory wheeze, decreased aeration
Heart rate, /min				
<3 years old	<120	120–140	141–160	>160
≥3 years old	<100	100–120	121–140	>140
Respiratory rate, /min				
<6 years old	≤30	31–45	46–60	>60
≥6 years old	≤20	21–35	36–50	>50

In the MPIS score, 6 different categories are evaluated: (1) oxygen saturation on room air, (2) accessory muscle use, (3) inspiratory-to-expiratory flow ratio, (4) degree of wheezing,(5) heart rate, and (6) respiratory rate. Three of these variables are objective and 3 are subjective. For each of these 6 measurements or observations, a score of 0 to 3 is assigned, resulting in a possible minimum score of 0 and a maximum score of 18.

Reference: Carroll CL, Sekaran AK, Lerer TJ, Schramm CM. A modified pulmonary index score with predictive value for pediatric asthma exacerbations. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2005 Mar;94(3):355–9.

APPENDIX (VII): INSTITUTIONAL REVIEW BOARD AND ETHICS COMMITTEE APPROVAL

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD
CHRISTIANMEDICALCOLLEGE,
BAGAYAM, VELLORE 632002, TAMIL NADU, INDIA

Ref: FG/9176/11/2014

January 02, 2015

Mr. Robby Pria Sundersingh
The Treasurer
Christian Medical College,
Vellore.

Dear Mr. Robby Pria Sundersingh,

Sub: **Fluid Research grant project:**
Montelukast for acute asthma exacerbation in children 5 years - 15 years-A randomized double blind placebo controlled study.
Dr. C. Rahul Reddy, Dr. Sneha Varkki, Paediatrics, Dr. Nithya, Child Health, CMC, Vellore.

Ref: IRB Min. No. 9176 dated 26.11.2014

The Institutional Review Board at its meeting held on November 26th 2014 vide IRB Min. No. 9176 accepted the project *for a total sum of 35,000/- INR (Rupees Thirty Five Thousand only) will be granted for 9 months. If overspent the excess should be debited form the respective departmental or Special funds.* Kindly arrange to transfer the sanctioned amount to a separate account to be operated by Dr. C. Rahul Reddy (rahulreddychintala@gmail.com) and Dr. Sneha Varkki (Child3@cmcvellore.ac.in)

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD,MNAMS,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

CC: Dr. C. Rahul Reddy, Child Health, CMC.
Dr. Sneha Varkki, Child Health, CMC
File

APPENDIX VIII. PHARMACY LETTER

Ref: *PhjDCj803j15*

Pharmacy Services, CMC

16.09.2015

To

Dept. of Child Health
Christian Medical College
Vellore - 4

Dear Dr

This is with reference to your e-mail dated 11.09.2015 regarding queries on the preparation of Montelukast Oral Suspension made for your project.

1) Preparation of Placebo oral suspension

The name of non-medicinal excipients and the composition of placebo oral suspension are given below:

- Microcrystalline cellulose
- Propylene glycol
- Potassium sorbate
- Citric acid
- Sucrose
- Sodium metabisulfite
- Silica gel
- Methyl paraben sodium
- Propyl paraben sodium
- Vanillin (flavor)
- Tartrazine yellow (color)
- Purified water, sufficient quantity

2) Preparation of Montelukast oral suspension

Required quantities of drug tablets are powdered and the suspension is made with all the excipients used for making placebo oral suspension.

3) Analysis of Montelukast Oral Suspension

Montelukast oral suspension was prepared and supplied to you in two installments. The samples were sent to external analytical laboratory in Chennai *(Mis.* ATOZ analytical laboratory) for the identification and assay of Montelukast present in the suspension. The quality of the suspension analyzed complies with specifications. I have enclosed copies of the analysis report for your reference.

I hope the information provided will help you in writing the thesis. If you have any queries further, please contact me.

Thank you

Yours Sincerely,

S. A~~'

- II>/o<7("~

Dr. S. Annadurai
Professor & In-charge
Manufacturing Division

Encl: as above.

c.c: Head, Pharmacy Services .

. ad/sep

APPENDIX IX. CERTIFICATE OF ANALYSIS OF DRUG

ATOZ PHARMACEUTICALS PVT. LTD.

12, Balaji Nagar, Ambattur, Chennai - 600 053. Phone : 26582985, 26585855.

TOZ
al Services

Form : 39

Certificate of Analysis

Approval No. : 34

(As per Drugs & Cosmetics Act, 1940 and the rules made there under)

ATOZ
Analytical Services

of Manufacturer from whom sample received with Mfg. Lic. No.

CHRISTIAN MEDICAL COLLEGE.
IDA SCUDDER ROAD.
VELLORE-632 004.
3.INDIA.

Report No. : F14/D/03/72

Date : 02/12/14

. No. :
nce Number and Date of the letter :
of Drug/Cosmetic/Raw Material
rting to be contained in the sample :
of Raw Material/Final Product (in bulk) MONTELUKAST SUSPENSION
roduct (in finished pack) "WATER BASED"
iginal Manufacturer's / Supplier Name (in case of -
aterials and Drugs repacked) :
SELF

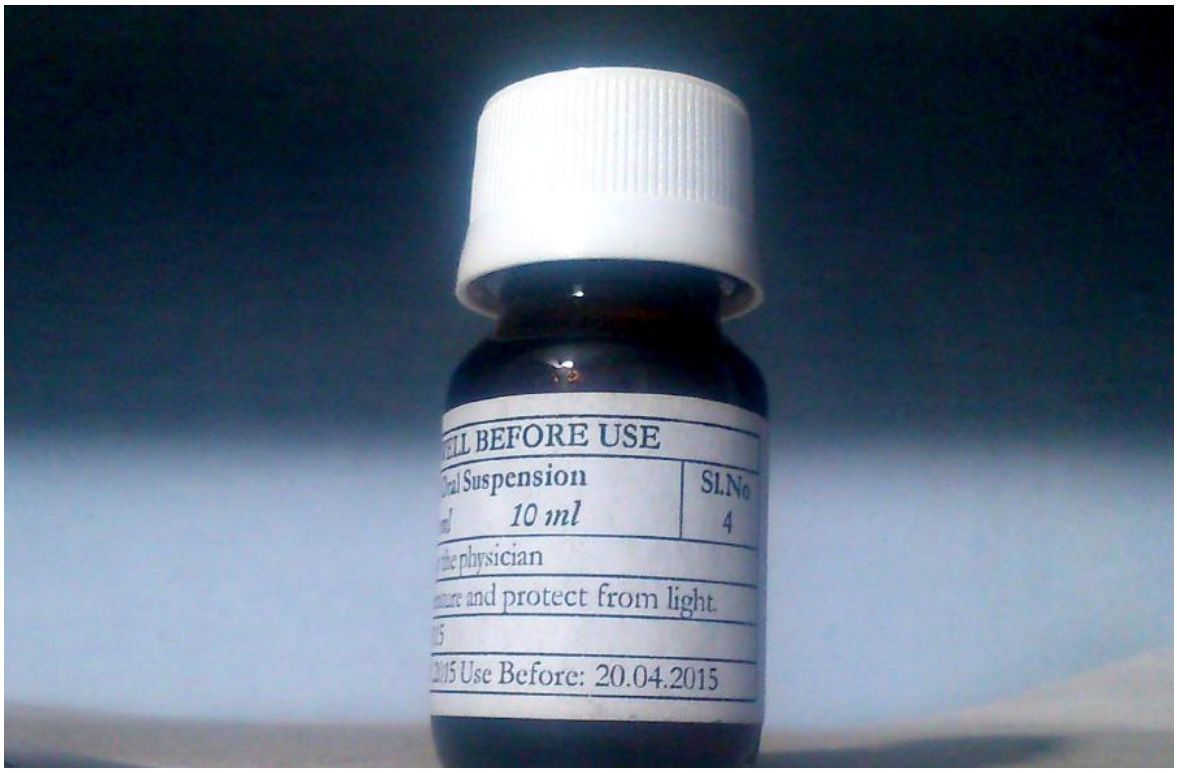
3.Date of Receipt of the Sample : 29/11/14

atch No. / ontrol No.	(c) Total Quantity represented by the sample	(d) Date of Manufacture	(e) Date of Expiry	(f) Quantity of Sample submitted
7112014B	-	27.11.14	25.02.15	40 ML

of Analysis — SAMPLE NOT DRAWN BY US

DESCRIPTION	: A YELLOW COLOURED SUSPENSION		
pH	: 4.63		
WEIGHT / ML	: 1.09282 GM		
IDENTIFICATION	: POSITIVE FOR THE PRESENCE OF MONTELUKAST SODIUM		
EACH 5 ml CONTAINS	: AS PER ANALYSIS	LABEL CLAIM	LIMIT
MONTELUKAST SODIUM	: 4.839mg.(96.782%)	5mg	90%----110%

APPENDIX X. PHOTOGRAPH OF STUDY DRUG PREPARED BY PHARMACY



APPENDIX (XI): DATA SAFETY MONITORING BOARD APPROVAL

OFFICE OF THE VICE-PRINCIPAL (RESEARCH)
CHRISTIAN MEDICAL COLLEGE, VELLORE – 632 002

To
Dr. C. Rahul Reddy
Department of Paediatrics
Christian Medical College, Vellore

26th August 2015

Ref. IRB. Min. No: 9176 dated 26-Nov-2014

Dear Dr. C. Rahul Reddy,

The Data Safety Monitoring Board (DSMB) of the Christian Medical College, Vellore, reviewed and discussed your project entitled *"Montelukast for acute asthma exacerbation in children 5 years - 15 years-A randomized double blind placebo controlled study."* on 21st August, 2015 in the E-Learning Conference Room, Asha building, Christian Medical College & Hospital, Vellore 632 004.

The committee reviewed the proposal and raised queries:

1. Target: 104 subjects. 18 completed study. 18 are active. These terms are mutually exclusive amend to read 18 completed.
2. Document the number of casualty admissions.
3. PI and Guide were informed about the SAE policy.

Dr. C. Rahul Reddy and Dr. Sneha Varkki were present during the meeting and satisfactorily responded to the queries raised by the Members.

The proposal may be ACCEPTED AFTER receiving the suggested modifications and answers to the queries.

The Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmchvellore.edu/static/research/Index.html.

Thank you.

Yours Sincerely,

Dr. Nihal Thomas,
Addl. Vice Principal (Research) & (Convener) Data Safety Monitoring Board - DSMB
CC: Dr. Sneha Varkki, Paediatrics

Telephone: +91 (0) 416 228 4294
Email: research@cmcvellore.ac.in / researchothers@cmcvellore.ac.in

APPENDIX (XII): RANDOMISATION CODE

arm	group	serial no
placebo	2	001
montelukast	1	002
placebo	2	003
montelukast	1	004
placebo	2	005
montelukast	1	006
montelukast	1	007
placebo	2	008
montelukast	1	009
placebo	2	010
montelukast	1	011
placebo	2	012
placebo	2	013
montelukast	1	014
placebo	2	015
montelukast	1	016
montelukast	1	017
placebo	2	018
placebo	2	019
montelukast	1	020
placebo	2	021
montelukast	1	022

APPENDIX XIII. DATABASE

stno	nm	hsno	age	sex	add	wt	onst	dur	uri	inh	ar
1	kiran kumar	751683f	11	1	arni	30	5	3	TRUE	TRUE	FALSE
2	madhav sai	687144d	11	1	chittoor	32	5	3	TRUE	FALSE	FALSE
3	mrinmoy patra	964995d	5	1	west bengal	17	2	2	TRUE	FALSE	TRUE
4	sanjay	832327c	10	1	vellore	10	5	1	TRUE	FALSE	FALSE
5	krishna	941669f	9	1	Bagayam	21	1	4	TRUE	FALSE	FALSE
6	harini	941902f	7	2	senur	16	6	2	TRUE	FALSE	FALSE
7	gokul	944251f	9	1	walaja	25	1	2	TRUE	FALSE	FALSE
8	dharun	857201f	9	1	vellore	21	1	1	TRUE	FALSE	FALSE
9	dhruba roy	240594g	9	1	assam	27	5	2	FALSE	FALSE	FALSE
10	vidhya sri	241094g	9	2	kancheepuram	21	2	2	TRUE	FALSE	FALSE
11	immanuel	039771c	14	1	vellore	54	1	3	TRUE	TRUE	FALSE
12	ariyan shaw	261942g	8	1	west bengal	23	1	1	FALSE	FALSE	FALSE
13	karthik kumar	234356g	13	1	vellore	31	2	4	TRUE	TRUE	FALSE
14	pradip majumdar	256862g	15	1	darjeeling	34	1	5	FALSE	FALSE	FALSE
15	shyam	696169f	6	1	kancheepuram	19	2	3	TRUE	TRUE	FALSE
16	vendamani's baby	499829c	12	1	vellore	29	1	2	FALSE	FALSE	FALSE
18	rukesh kumar	208055g	10	1	walaja	31	1	1	TRUE	FALSE	TRUE
19	mahalakshmi's baby	200486d	7	1	vellore	20	3	3	TRUE	TRUE	FALSE
17	sagarika ghosh	568311c	11	2	west bengal	55	1	5	TRUE	TRUE	FALSE
20	aparna	449611f	9	2	vellore	22	3	2	TRUE	TRUE	TRUE
21	shaailesh	651060d	5	1	vellore	21	2	1	TRUE	FALSE	FALSE
22	yuvesh kumar	403176f	9	1	vellore	22	2	7	TRUE	TRUE	TRUE

stno	fh	dt1	dt2	dt3	dt4	oxy	ivf	abx	sp01	sp02	sp03	amu1
1	TRUE	09/02/2015	18:00	10/02/2015	18:00	FALSE	FALSE	FALSE	0	0	0	0
2	FALSE	20/02/2015	13:30	21/02/2015	13:30	FALSE	FALSE	TRUE	1	0	0	2
3	TRUE	27/02/2015	18:00	28/02/2015	18:00	FALSE	FALSE	FALSE	0	0	0	0
4	FALSE	17/03/2015	03:45	18/03/2015	03:45	TRUE	TRUE	TRUE	2	0	0	2
5	FALSE	30/03/2015	11:40	31/03/2015	11;40	FALSE	TRUE	TRUE	0	1	0	2
6	FALSE	15/04/2015	10:00	16/04/2015	10:00	FALSE	FALSE	FALSE	0	0	0	2
7	FALSE	13/05/2015	09:30	14/05/2015	09:30	FALSE	FALSE	TRUE	0	0	0	2
8	FALSE	18/06/2015	16:40	19/06/2015	16:40	FALSE	FALSE	FALSE	0	0	0	2
9	FALSE	11/08/2015	17:30	12/08/2015	17:30	FALSE	FALSE	FALSE	0	0	0	1
10	FALSE	15/06/2015	16:00	16/06/2015	16:00	FALSE	FALSE	FALSE	0	0	0	1
11	TRUE	02/07/2015	11:00	03/07/2015	11:00	FALSE	FALSE	FALSE	0	0	0	0
12	FALSE	10/07/2015	12:00	11/07/2015	12:00	FALSE	FALSE	FALSE	0	0	0	2
13	TRUE	13/07/2015	12:30	14/07/2015	12:30	FALSE	FALSE	TRUE	1	1	0	2
14	FALSE	14/07/2015	16:00	15/07/2015	16:00	FALSE	FALSE	FALSE	0	0	0	1
15	FALSE	27/07/2015	20:00	28/07/2015	20:00	FALSE	FALSE	FALSE	0	0	0	1
16	FALSE	30/07/2015	12:20	31/07/2015	12:20	FALSE	FALSE	FALSE	2	1	0	1
18	TRUE	06/08/2015	16:45	07/08/2015	16:45	FALSE	FALSE	FALSE	0	0	0	1
19	TRUE	17/08/2015	15:30			FALSE	FALSE	FALSE	0	0	0	1
17	FALSE	02/09/2015	14:00	03/09/2015	14:00	FALSE	FALSE	FALSE	0	0	0	0
20	FALSE	25/08/2015	09:45			FALSE	FALSE	TRUE	2	1	0	0
21	TRUE	01/09/2015	12:00	02/09/2015	12:00	FALSE	FALSE	TRUE	1	0	0	2
22	TRUE	31/08/2015	18:00	01/09/2015	18:00	FALSE	FALSE	FALSE	0	0	0	1

stno	amu2	amu3	ier1	ier2	ier3	whz1	whz2	whz3	hr1	hr2	hr3	rr1	rr2	rr3	mpis1	mpis2	mpis3	pef1
1	0	0	2	1	0	2	0	0	1	1	0	2	1	1	7	2	1	100
2	1	0	1	0	0	2	2	0	2	0	0	2	1	0	10	4	0	80
3	0	0	2	1	0	1	1	0	2	2	1	1	1	0	6	5	1	65
4	0	0	2	1	1	1	0	0	2	2	0	2	0	0	11	3	2	50
5	1	0	3	1	0	2	1	1	1	0	0	2	1	0	11	5	1	60
6	0	0	2	1	0	2	1	0	2	1	0	2	1	0	8	4	0	60
7	0	0	2	0	0	2	1	0	3	1	0	2	2	0	11	4	0	100
8	1	0	2	0	0	1	0	0	1	1	0	1	0	0	7	2	0	60
9	0	0	3	0	0	2	0	0	1	1	1	1	1	0	8	2	0	70
10	0	0	1	0	0	1	0	0	1	0	1	1	1	0	5	1	1	70
11	0	0	2	1	0	2	0	0	0	0	0	2	1	0	6	2	0	190
12	1	0	1	1	0	1	0	0	1	0	0	1	1	0	6	3	0	100
13	2	0	2	2	0	2	2	0	2	2	2	2	2	1	11	11	3	100
14	0	0	1	0	0	2	0	0	1	1	1	0	1	1	5	2	2	160
15	0	0	1	0	0	1	0	0	1	1	0	2	1	0	6	2	0	100
16	2	0	2	2	0	1	2	0	1	1	0	3	2	1	11	10	1	110
18	0	0	1	1	1	1	0	1	2	2	0	1	0	1	6	3	3	80
19	0	0	2	0	0	2	0	0	0	0	0	2	1	0	7	1	0	120
17	0	0	1	0	0	1	0	0	3	1	0	1	0	0	6	1	0	120
20	0	0	1	0	0	2	1	0	2	2	1	0	0	0	7	4	1	120
21	0	0	1	1	1	2	0	1	2	3	1	1	0	1	9	4	4	105
22	0	0	1	0	0	2	0	0	1	0	1	1	1	1	6	1	2	120

stno	pef2	pef3	pef4	vas1	vas2	vas3	vac1	vac2	vac3	hdach	abdpn	dzn	drh	vmt	urt
1	150	210	300	6	7	8	7	8	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
2	110	180	300	3	7	9	1	6	8	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
3	80	100		5	6	8	7	8	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
4	120	150	150	2	7	8	2	7	8	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
5	80	120	170	1	7	7	3	7	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
6	100	120	120	3	8	9	1	7	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
7	200	200	230	3	8	9	1	9	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
8	160	160	200	7	9	10	6	9	10	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
9	150	150		5	6	7	5	6	8	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
10	100	100	150	5	7	8	6	9	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
11	250	250	300	8	9	10	8	9	10	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
12	150	150		5	7	8	5	7	8	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
13	150	200	200	1	6	9	3	7	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
14	220	280		1	7	9	1	7	9	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE
15	100	120	150	2	4	8	2	4	8	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
16	130	160	180	1	7	9	1	7	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
18	100	170	200	7	8	9	7	8	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
19	150	150	160	3	8	9	5	8	9	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE
17	150	150		6	8	9	6	8	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
20	140	150	210	3	6	9	6	8	9	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE
21	100	120	130	6	9	9	5	8	9	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
22	140	150	180	3	6	8	5	6	8	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE

stno	str	neb	mdi	adm	liv
1	FALSE	3	7	FALSE	TRUE
2	TRUE	8	4	FALSE	TRUE
3	FALSE	0	9	FALSE	TRUE
4	TRUE	8	5	FALSE	TRUE
5	FALSE	3	8	FALSE	TRUE
6	FALSE	3	10	FALSE	TRUE
7	TRUE	3	11	FALSE	TRUE
8	FALSE	0	12	FALSE	TRUE
9	FALSE	3	9	FALSE	TRUE
10	FALSE	0	10	FALSE	TRUE
11	FALSE	3	9	FALSE	TRUE
12	FALSE	0	9	FALSE	TRUE
13	TRUE	9	4	FALSE	TRUE
14	FALSE	0	11	FALSE	TRUE
15	FALSE	0	13	FALSE	TRUE
16	FALSE	0	10	FALSE	TRUE
18	FALSE	1	10	FALSE	TRUE
19	FALSE	1	2	FALSE	TRUE
17	FALSE	0	3	FALSE	TRUE
20	FALSE	3	9	FALSE	TRUE
21	TRUE	8	8	FALSE	TRUE
22	TRUE	0	9	FALSE	TRUE